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RADIUM THERAPY

RADIUM THERAPY

BY

FRANK EDWARD SIMPSON, A.B., M.D.

PROFESSOR OF DERMATOLOGY, CHICAGO POLICLINIC; ADJUNCT CLINICAL PROFESSOR OF DERMATOLOGY, NORTHWESTERN UNIVERSITY MEDICAL SCHOOL; ATTENDING DERMATOLOGIST TO MERCY HOSPITAL, ALEXIAN BROTHERS HOSPITAL, HENROTIN HOSPITAL, ETC.; FORMER PRESIDENT AMERICAN RADIUM SOCIETY; FORMER VICE CHAIRMAN, SECTION OF DERMATOLOGY AND SYPHILOLOGY, AMERICAN MEDICAL ASSOCIATION; DIRECTOR OF THE FRANK EDWARD SIMPSON RADIUM INSTITUTE.

WITH 166 ORIGINAL ENGRAVINGS

ST. LOUIS

C. V. MOSBY COMPANY

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TO

M. B. L. S.

MY WIFE

57705

PREFACE

The completed manuscript of this book was given to the publishers on July 6, 1921. The delay in publication, due to unusual industrial conditions, has enabled me to make some minor corrections in the clinical part of the work and to bring the bibliography up to date.

A survey of the literature referred to in the bibliography, which I have tried to make comprehensive rather than critical, indicates the widespread interest in radium therapy. Unfortunately, lack of space has made it possible to mention specifically in the text the work of only a few of the authors listed in the bibliography.

The immense task of verifying all of the references in the bibliography has been accomplished only through the assistance of Mr. Robert J. Usher, Mr. William L. Teal, Miss Beryl L. Kanagy and Miss Hazel B. Kraft and I desire to express my thanks for their invaluable help.

I wish also to express at this time my appreciation of the great kindness of several of my colleagues and friends. Dr. Paul Degrais and Dr. Bellot of Paris have generously loaned me the drawings of microscopic sections, taken from their own immense material, which are reproduced in this book. Dr. George Winchester has prepared the framework of the chapter on the collection and purification of the emanation for therapeutic purposes. Mr. L. W. Taylor has made the schematic drawing of the emanation apparatus and has constructed the emanation decay table inserted in Chapter IV. Dr. C. H. Viol has loaned me the photograph of the Debierne-Duane-Failla emanation apparatus which is reproduced in the book. He has also read over the sections on the physics of radium and made valuable suggestions. Mr. James Eglin has carried out the actual work involved in the experiments on the absorption of gamma radiations in water, and has made the mathematical calculations used in the contruction of the tables in the chapter on dosage. Miss A. B. Hepburn, formerly physicist in our laboratory and Mr. Melvin Mooney, the present physicist, have also made valuable suggestions relative to the physics of radium. I am also indebted to Mr. Mooney for the schematic drawing of the electroscope. I wish to take this occasion to thank the publishers for their kind and unfailing cooperation.

It is hoped that the book may be of interest, not only to those actually engaged in radium therapy, but to all physicians, and that it may serve as a reflex of the current practice in this branch of medicine.

F. E. S.

CHICAGO, March, 1922.

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RADIUM THERAPY

CHAPTER I

THE RADIOACTIVE SUBSTANCES

THE DISCOVERY OF RADIOACTIVITY

Soon after Roentgen's discovery in 1895 of the x-rays, several physicists began to experiment with various substances to determine whether similar rays might be emitted by chemical bodies spontaneously. Poincaré suggested that the production of x-rays, which penetrated matter opaque to ordinary light, might be connected with the phosphorescence and fluorescence excited by the cathode rays in the glass of the vacuum tube. It was natural at first, therefore, to examine substances that fluoresced under the action of ordinary light. Prof. Henri Becquerel of Paris soon found that the fluorescent salts of uranium emitted radiations that passed through a thin layer of silver and affected a photographic plate. It was at first supposed that the emission of these peculiar radiations was in some way connected with the fluorescent properties exhibited by some of the uranium compounds. Further experiments proved, however, that the nonfluorescent salts and the metal uranium itself, which is also nonfluorescent, emitted the radiations. From this observation Prof. Becquerel concluded that the rays were due to the element uranium and were independent of phosphorescence or fluorescence. The announcement of this new property of matter—so-called radioactivity—was made to the Academy of Sciences at Paris on February 24, 1896. Later Prof. Becquerel showed that uranium radiations like x-rays were capable of discharging electrified bodies such as the electroscope. Rutherford, in 1899, demonstrated that this effect was due to the "ionization" of the air in the electroscope by the radiations. This phenomenon will be referred to more fully in our description of the method of measuring the gamma-ray activity of radium.

THE DISCOVERY OF POLONIUM, RADIUM, MESOTHORIUM RADIOTHORIUM AND IONIUM

Using the electroscopic method of investigation, different physicists then examined various other substances in order to determine whether they were radioactive. G. C. Schmidt and Mme. Curie, working inde-

pendently, discovered in 1898 that thorium, an element derived from monazite and previously well known, possessed radioactive properties. M. and Mme. Curie then found that certain uranium ores exhibited a greater degree of radioactivity than could be accounted for by the presence of either uranium or thorium. They assumed, therefore, that some unknown element or elements were present in the ores. Their labors finally resulted in the discovery of polonium which was named from Mme. Curie's native land, and later (1898) of radium. Polonium is now known to be merely Radium F., one of the decay products of radium itself. In 1900, Debierne obtained from pitchblende another radioactive product which he called "actinium" and in 1905 Hahn isolated mesothorium and radiothorium. Ionium was discovered in 1907 by Boltwood. Altogether more than 30 radioactive substances are now known.

TRANSFORMATION OF THE RADIOACTIVE SUBSTANCES

It was at first supposed that the radioactivity of uranium, thorium and radium was a permanent attribute. Later, evidence of the decay and recovery of radioactivity was noted. Now all accept the hypothesis first advanced by Rutherford and Soddy which explains radioactivity as a spontaneous process of atomic transformation. This process goes on at a regular rate for each radioactive substance and is accompanied by the emission of rays and the production of new forms of matter, these new elements in time transforming, until finally a stable atomic form is reached. These changes go on with greatly varying degrees of rapidity. Some of the radioactive bodies are transforming themselves so slowly that no change in their radioactivity can be detected over a period of several years. Their radioactivity, therefore, is relatively constant. To this group belong uranium, ionium, radium and thorium. Other radioactive bodies, of which mesothorium 2 and thorium X are examples, transform themselves very quickly and cease to emit rays after a few hours or days. The rate of transmutation is constant for any given substance, but differs for the different radio-elements. The rate at which a substance decays follows an exponential law; i.e., the rate at which a substance is decaying at a given instant is proportional to the amount present at that instant. It is this factor of proportionality that is constant for any particular substance. The rate of loss of activity is usually spoken of in terms of the "period," or more properly the "half decay period" both expressions being used in an identical manner. The period of radium is approximately 1680 years. By this is meant that after 1680 years, one half of the original number of atoms remains untransformed; after 3360 years (2x1680) one fourth remains; after 5040 years (3x1680) one eighth remains, and so on indefinitely. Radioactive transformations differ from ordinary chemical reactions in that the rate of degeneration or change

of one radioactive substance into another cannot be altered by any known physical or chemical means. The rate of transformation remains the same throughout extremes of temperature and pressure. As each radioactive substance transforms, it gives off radiations, which are of three different kinds and are known as alpha, beta and gamma rays. These will be described in a subsequent chapter.

THE RADIOACTIVE FAMILIES

At the present time, three parent substances are known—uranium, actinium, and thorium—each of which transforms itself into a series of substances until an end or stable product is reached. There are thus formed three families or series of radioactive substances, viz., the uranium series, the actinium series, and the thorium series. The knowledge of the fact that actinium and its decay products are always present in uranium minerals, leads to the belief that this product represents a small fraction (3 per cent) of the "uranium 2" atoms which transform into "uranium Y" rather than into ionium. We may interpolate a table at this point showing the members of each series of radioactive bodies, the rays each substance emits and its half value, i.e., the time required for ½ of a given quantity to disappear by spontaneous transformation.

TABLE 1

URANIUM-RADIUM FAMILY

NAME	ATOMIC WEIGHT	HALF DECAY PERIOD	RADIATION
Uranium I	238	5 billion years	alpha
Uranium X_1	234	24.6 minutes	beta+gamma
Uranium X_2	234	1.15 minutes	beta+gamma
Uranium$_2$	234	About 1,000,000 years	alpha
Ionium	230	About 100,000 years	alpha
Radium	226	1680 years	alpha
Radium Emanation (Niton)	222	3.85 days	alpha
Radium A	218	3 minutes	alpha
Radium B	214	26.8 minutes	beta+gamma
Radium C (99.97%) (0.03%)	214	19.5 minutes	beta+gamma (alpha)
Radium C_2 (side reaction 0.03%)	210	1.4 minutes	beta+gamma
End 0.03%	210	.....	.....
Radium C' (Main reaction 99.97%)	214	0.000001 seconds	alpha
Radium D	210	16.5 years	soft beta
Radium E	210	5.0 days	soft beta
Radium F (Polonium)	210	136 days	alpha
Radium G (End Product)	206	.....	No rays— Atoms stable

TABLE II

ACTINIUM FAMILY

NAME	ATOMIC WEIGHT	HALF DECAY PERIOD	RADIATION
3% of Uranium II	234	About 1,000,000 years	alpha
Uranium Y	230	1.5 days	beta
Protactinium	230	Estimated 1,200 to 180,000 years	alpha
Actinium	226	About 30 years	soft beta
Radioactinium	226	19.5 days	alpha
Actinium X	222	11.4 days	alpha
Actinium Emanation	218	3.9 seconds	alpha
Actinium A	214	0.002 seconds	alpha
Actinium B	210	36.1 minutes	beta+gamma
Actinium C	210	2.15 minutes	alpha
Actinium D	206	4.71 minutes	beta+gamma
End Product	206	.....	.....

TABLE III

THORIUM FAMILY

NAME	ATOMIC WEIGHT	HALF DECAY PERIOD	RADIATION
Thorium	232	23 billion years	alpha
Mesothorium$_1$	228	6.7 years	soft beta
Mesothorium$_2$	228	6.2 hours	beta+gamma
Radiothorium	228	1.9 years	alpha
Thorium X	224	3.64 days	alpha
Thorium Emanation	220	54 seconds	alpha
Thorium A	216	0.14 seconds	alpha
Thorium B	212	10.6 hours	beta
Thorium C$_1$	212	60 minutes	65% beta+gamma to ThC$_2$ 35% alpha to ThD
Thorium C$_2$ (Side Reaction)	212	Estimated 10^{-11} seconds	alpha
End	208	.....	.....
Thorium D (Main Reaction)	208	3.1 minutes	beta+gamma
End	208	.....	.....

CHAPTER II

RADIUM—ITS ORIGIN AND CHEMICAL NATURE

ORIGIN

Radium was first extracted by M. and Mme. Curie in the form of radium bromide from pitchblende residues, obtained from St. Joachimsthal in Bohemia. It was subsequently found to be present not only in all pitchblende ores, but also in all minerals containing uranium.

The work of McCoy, Boltwood and others has shown that in the very old uranium minerals there is a strict proportion between the uranium and radium content. For each 3,000,000 grams (three metric tons) of metallic uranium there is one gram of metallic radium. This is very strong corroborative evidence of the disintegration theory of Rutherford and Soddy, according to which uranium is the parent of radium. In uranium-containing minerals of more recent origin, the amount of radium is 30 to 40 per cent less for the same amount of uranium than in the older minerals. There is, however, no mineral or ore known, containing radium, which does not contain uranium.

URANINITE AND CARNOTITE

While many uranium-containing minerals are known, only two are of practical importance. These are uraninite and carnotite. In these ores, radium occurs in workable quantities.

Uraninite is found in Bohemia, Cornwall, Colorado and many other localities. This mineral occurs chiefly in an amorphous modification known as pitchblende, a dense black substance of variable composition and therefore not to be described by a single chemical formula. Pitchblende is essentially an oxide of uranium and contains in varying quantities nearly half of the known metals.

Carnotite is an ore of much greater practical importance than uraninite. It is the chief substance from which radium is now obtained. Large deposits of carnotite have been found in Colorado and Utah. In the "carnotite belt" of Colorado it has been estimated that there are at least eight million pounds of uranium. From this it has been estimated that there may be extracted at least 1000 grams of radium element.

Carnotite (named from the French chemist Carnot) was first described by two French mineralogists, Friedel and Cummenge, in 1899. It is a bright yellow powder composed of very minute crystals. Its chemical composition is very complex, but, when pure, it appears to be a potassium uranyl vanadate. It occurs in nature in sandstone formations. Average carnotite

sandstone contains about 1.5 per cent to 6 per cent U_3O_8 and this yields from 3.5 to 15 mg. of radium element per ton. The extraction of radium from carnotite ore or from other minerals is a very complicated process. For the separation of one gram of radium element, approximately 500 tons of chemicals and one thousand tons of coal are used. After a considerable amount of mechanical preparation (crushing of ore, etc.) and chemical treatment, the radium and barium are isolated together as radium barium chloride. From barium the radium is separated finally in the form of radium bromide, by a process of fractional crystallization.

From this salt, all the other salts (chloride, sulphate, carbonate, etc.) are prepared. Radium bromide and radium chloride are soluble while the sulphate and carbonate are insoluble in water.

In the radium solution contained in the glass flask from which radium emanation is to be extracted for therapeutic purposes the radium is in the form of soluble radium chloride.

For making the various therapeutic applicators (tubes, glazed plaques, toiles, etc.) the insoluble radium sulphate is used.

THE CHEMICAL NATURE OF RADIUM

Radium is to be regarded as a chemical element (symbol Ra.) belonging to the group of alkali earth metals, which comprises the elements barium, strontium, calcium and magnesium.

Demarçay found that radium gave a new and characteristic bright line spectrum similar to the spectra of barium, calcium and strontium. Its atomic weight, as determined by Mme. Curie, is 226.45. In its chemical behavior, radium is closely allied to barium, forming a series of analogous salts (bromide, chloride, sulphate, carbonate, etc.). It differs essentially from that element, however, in being radioactive. In general properties, it is analogous to the metals of the alkaline earths.

It was not until 1910 that radium was isolated by Mme. Curie and Debierne in a metallic state. It was then found to be a pure white metal showing the radioactive properties that would be expected on the assumption that radioactivity is an atomic phenomenon. It produced radium emanation and its activity increased at the theoretic calculated rate. Metallic radium changes quickly when exposed to the air. It reacts with water, decomposing it into hydrogen with the production of radium hydroxide.

THE OCCURRENCE OF RADIUM IN NATURE

Besides occurring in more or less concentrated form in various ores, radium is found throughout the earth's crust as one of the most widely distributed of substances. Strutt, Joly, Knocke, and others have detected it in minute quantities in volcanic rocks and in sea and river waters.

As to the natural occurrence of radium in the animal and vegetable tissues, experiments have been made by Lazarus-Barlow, Becquerel and others to determine this point. Evidence has been presented to show that radium in very minute quantities, but detectable by the electroscope, exists in human tissues. Lazarus-Barlow has sought to show that in human tissues affected by malignant disease a slightly larger quantity is present than in normal tissues. This hypothesis cannot be considered as established, and since no radium salt is absolutely insoluble, it is difficult to reconcile the concentration of radium in a tissue with any hypothesis that does not also involve the simultaneous increase in concentration of other elements such as calcium and magnesium, and if this be true, their chemical effects must also be considered.

Prof. Becquerel concluded that if radium or any other radioactive substance exists in plants, it is in such small quantities as to have no appreciable effect on their growth.

CHAPTER III

RADIUM EMANATION AND RADIOACTIVE DEPOSIT

THE DECAY OF RADIUM INTO RADIUM EMANATION

As has been previously said, radium atoms, like those of the other radioactive bodies, are not absolutely stable, but are constantly transforming and giving rise to a series of substances. The first of these substances is radium emanation—a gas known to chemists as "niton." The amount of this gas that is found in equilibrium with one gram of radium is a definite quantity and is known as the "curie." This is the unit of quantity and at standard temperature and pressure (0° C. and 760 mm.) may be expressed either as a unit of volume or of weight. At standard conditions, the volume of one curie is .63 cubic millimeters, and the weight is 6.2 micrograms. It is the heaviest gas known, having a density one hundred and eleven times that of hydrogen.

Chemically, radium emanation behaves as an inert gas, i.e., it forms no chemical combinations. It may be regarded as an analogue of the other "noble" gases, helium, neon, argon, krypton, and xenon.

Like radium itself, the emanation shows a characteristic spectrum, which is quite distinct, however, from that of its parent, radium. At low temperatures, the emanation can be condensed from the gas with which it is mixed. At very low pressures, the emanation condenses at –150° C., the temperature of liquid air. The boiling point at standard pressure is in the neighborhood of –65° C., and it has been found that the emanation cannot exist in the gaseous state below –71° C. Below this temperature, marked changes are observed in the appearance of the emanation.

When the radium atom decays into the radium emanation atom, it gives off an alpha particle, which is in reality a helium atom with a double positive charge. Since the atomic weight of helium is 4, it follows that the atomic weight of the emanation should be equal to the atomic weight of radium minus that of helium, or $226 - 4 = 222$. By actually weighing a known volume of the pure gas, Gray and Ramsay obtained the value of 224, which is very close to the theoretical atomic weight.

THE ABSORPTION OF RADIUM EMANATION BY DIFFERENT SUBSTANCES

Radium emanation may be absorbed to some extent by various solids, especially porous substances such as charcoal and particularly by cocoanut shell charcoal and platinum black.

Liquids have varying powers of absorbing the emanation. Fresh water absorbs more than salt water, while organic liquids absorb it more readily than either.

It was found by Rausch von Traubenberg that if air containing emanation was shaken up with water, the air and the water each soon contained a definite proportion of the emanation. In this respect the emanation follows Henry's law, for it is absorbed until a state of equilibrium is reached between the pressure of the emanation in the water and in the gas.

The term "coefficient of absorption" has been used to express the extent to which the emanation is soluble in liquids. This term may be defined as the ratio between the concentration of the emanation in the liquid and in the gas after equilibrium has been reached. The value of this coefficient may be determined experimentally by the method of von Traubenberg, i.e., by shaking up the liquid and the gas containing the emanation, and then measuring with the electroscope the relative amounts of emanation in the liquid and in the gas. It has been found that the coefficient of absorption decreases rapidly as the temperature of the water rises, at least between the limits of 0° and 39° C. At room temperature the coefficient has a value of .250 and at 37° C, a value of .165. The variation of absorption of radium emanation with the temperature of the water is of importance in connection with the emanation content of natural spring waters at various health resorts in England, Germany, the United States and other countries. The amount of radium emanation in different springs varies between 1 and 30 millicuries per million liters.

While claims have been put forward for the health-giving qualities of the waters of certain resorts, no direct connection can really be traced between the radium emanation in the springs and physiologic effects. Definite biologic effects that have been observed to follow the therapeutic administration of radium emanation or radium salts are due to quantities several million times greater than are to be found in any known natural springs.

THE DECAY OF RADIUM EMANATION INTO RADIOACTIVE DEPOSIT

Unlike the atoms of radium, which is a comparatively stable substance, the radium emanation atoms are very unstable and decay at a rapid rate to form atoms of a third substance known as Radium A. This change follows a simple exponential law, the half value period of radium emanation being 3.85 days. The transformation is thus so rapid that in about thirty days practically all of a given quantity of radium emanation

will have decayed. Later we shall insert a table showing the rate of decay of the emanation.

When the emanation atom transforms, it gives off an alpha particle or ray. This particle is actually an atom of helium, which is also a gas. The substance remaining is an atom of a solid known as Radium A. Radium A in turn gives off an alpha particle and becomes Radium B. Radium B gives off a beta particle and becomes Radium C. Radium C in turn disintegrates but in a more complex manner than the other products. Radium C may transform itself in two ways. A very small proportion gives off an alpha particle and becomes Radium C_2. This latter substance is a branch product and so far as we know comes to an end quickly. The remainder, and larger portion, of Radium C gives off beta and gamma rays and becomes Radium C_1, which in turn gives off an alpha particle and becomes Radium D. Radium D gives off a beta ray and becomes Radium E, and this product by loss of a beta ray transforms to RaF, which is also known as polonium. Polonium then gives off an alpha particle and becomes the end product of the series, or Radium G, a substance chemically indistinguishable from lead, but having an atomic weight of 206 while the atomic weight of ordinary lead is 207.1.

THE RADIOACTIVE DEPOSIT

The series of substances from RaA to RaF constitutes the so-called radioactive deposit. This latter term was derived from the fact that these substances are deposited on the walls of the tube or other container when the radium emanation, sealed in the tube, decays. The radioactive deposit may be considered as being composed of two groups of substances, the one group being known as that of "rapid change" and the other group as that of "slow change." Radium A, B, C constitute the radioactive deposit of rapid change, their half value periods being 3 min., 26.7 min., and 19.5 min., respectively; radium D, E, and F constitute the radioactive deposit of slow change, their half value periods being 16.5 years, 5 days, and 136 days respectively. The penetrating radiations used therapeutically are derived from the active deposit of rapid change and especially from Radium C.

When a radium salt, such as radium sulphate, is sealed in a glass tube, it is evident that the emanation which is forming continuously cannot escape. At the same time the emanation is also disintegrating to form the series of products just described. After a certain time (about six weeks) the two processes have reached a stage at which the number of radium atoms disintegrating per second to produce emanation atoms equals the number of emanation atoms transforming to RaA. When this takes place, the radium is said to be in equilibrium with its emanation. It is not necessary, however, for the formation of the active de-

posit that the tube should contain radium at all. If the radium emanation alone is introduced into the tube and the tube is sealed, the active deposit is formed in precisely the same manner. When the emanation has all decayed, the active deposit of course ceases to form and the radioactivity of the tube is at an end so far as its therapeutic efficiency is concerned. As a matter of fact, radium D, E and F are still contained in the tube, but as their transformation is very slow, and as the gamma rays produced by them are of feeble intensity, these products are not of therapeutic interest so far as the local application of radium is concerned.

The Atomic Disintegration Theory of Rutherford and Soddy

The disintegration theory of Rutherford and Soddy explains in a rational manner the transformation which radium and the other radioactive substances undergo. According to this theory substances exist in nature whose atoms, unlike those of most elements, are not stable but are constantly undergoing spontaneous disintegration. These are known as radioactive substances. The rapid disintegration or "explosion" of the atoms of such substances results in a rearrangement of the electrons composing the atoms. In a given time a certain definite proportion of all the atoms of a radioactive substance becomes unstable and breaks up. An alpha particle or ray or beta and gamma rays are given off in the process of disintegration. In a few cases, as in the case of actinium, which transmutes into radioactinium, disintegration of the atom apparently takes place without rays being given off. There is chemical evidence that leads to the belief that in these "rayless" changes there is really emitted a low speed beta ray which because of its low velocity escapes detection. When an alpha particle is given off, as a consequence of the disintegration of the atom, the resulting atom is always lighter than its predecessor and possesses different physical and chemical properties. This is well illustrated by radium and its next transformation product, radium emanation, which are strikingly dissimilar, as we have seen.

From this viewpoint, we may now consider the breaking up of the radium atom to form the radium emanation atom, of the radium emanation atom to form the atom of radium A, etc. In the radium series there are 5 substances that give off alpha particles (helium atoms) as they disintegrate. These are, in order of occurrence, Radium, Radium emanation, Radium A, Radium C, and Radium F. Assuming the atomic weight of radium to be 226 and that of helium to be 4, the final atom produced when Radium F disintegrates should have an atomic weight of 226 less 20 (i.e., 5 x 4) or 206. This is slightly less than the atomic weight of lead and it is an isotope of this metal that is the final product in the radium disintegration series. In Table IV this point is made clear and certain other data are given for reference.

TABLE IV

RADIUM SERIES	ATOMIC WEIGHT	WEIGHT PER GRAM OF RADIUM	HALF-VALUE PERIOD	RADIATION	RANGE OF ALPHA RAYS AT 15° C.
Radium	226	1 gram	1680 years	alpha	3.30 cm.
Radium Emanation	222	5.7×10^{-6} gram	3.85 days	alpha	4.16 cm.
Radium A	218	3.1×10^{-9} gram	3.0 minutes	alpha	4.75 cm.
Radium B	214	2.7×10^{-8} gram	26.8 minutes	beta+gamma	.....
Radium C	214	2.0×10^{-8} gram	19.5 minutes	beta+gamma (alpha)	6.57 cm.
Radium C_2	...	.....	1.4 minutes	beta+gamma	.....
Radium D	210	8.6×10^{-3} gram	16.5 years	soft beta	.....
Radium E	210	7.1×10^{-6} gram	5.0 days	soft beta	.....
Radium F	210	1.9×10^{-4} gram	136 days	alpha	3.77 cm.
Radium G (End Product)	206	.....	.....	.....	No rays Atoms stable

CHAPTER IV

THE TECHNIC OF THE PREPARATION OF RADIUM EMANATION FOR THERAPEUTIC USE AND THE METHOD OF MEASURING ITS GAMMA RAY ACTIVITY

THE PREPARATION OF THE EMANATION

Radium emanation in tubes or applicators instead of the radium itself as a source of therapeutic radiations appears to have been used first in 1912 by the London Radium Institute. The Debierne-Duane apparatus (Fig. 1) as modified by Failla of New York is used by the writer for the extraction, purification, and concentration of the emanation. This apparatus consists essentially of two modified mercury pumps of the Toepler type, familiar to physicists. The first pump draws the accumulated gases from the flask containing the radium solution and introduces them into the purification chamber. The second pump withdraws the purified emanation and concentrates it in a capillary glass tube. The radium in the form of radium chloride is dissolved in about two ounces of water to which has been added a small amount of dilute hydrochloric acid to prevent precipitation of the salt. From a practical point of view not less than ½ gram of radium element can be utilized economically in this manner.

The glass flask containing the radium solution is kept in a suitable safe, and rests in a porcelain lined lead vessel in order to minimize the possibility of loss. The radium flask is not shown in the diagram but is connected by means of a glass tube (*1*, Fig. 2) to the pumping system of the emanation apparatus as shown in Fig. 2.

Vessel 4 (Fig. 2) is ordinarily kept partly filled with mercury in order to prevent the entrance of emanation. If the emanation were allowed to stand in this vessel it would cover the walls with the active deposit and since the surface of the vessel is quite large, the operator would find it necessary to shield himself from the bombardment of the rays.

The emanation that is formed by the disintegration of the radium is not the only gas formed in the solution. The radium rays, continually bombarding the water molecules, cause a decomposition of the water into its constituents, hydrogen and oxygen. These two gases form by far the largest part of all the gases produced. The total volume of all the different gases is many times the volume of the emanation. In order to concentrate the emanation into a small volume at a pressure of, e.g., 20 cm. of mercury, the foreign gases must, for the most part, be removed. In order to accomplish this, all the gases in the radium flask are pump-

over into the purification chamber *9*, *10*, and *11*, Fig. 2. Here the sodium hydroxide (*9*), and phosphorus pentoxide (*11*) absorb carbon dioxide, moisture, etc., while the heated copper oxide spiral (*10*) causes the hydro-

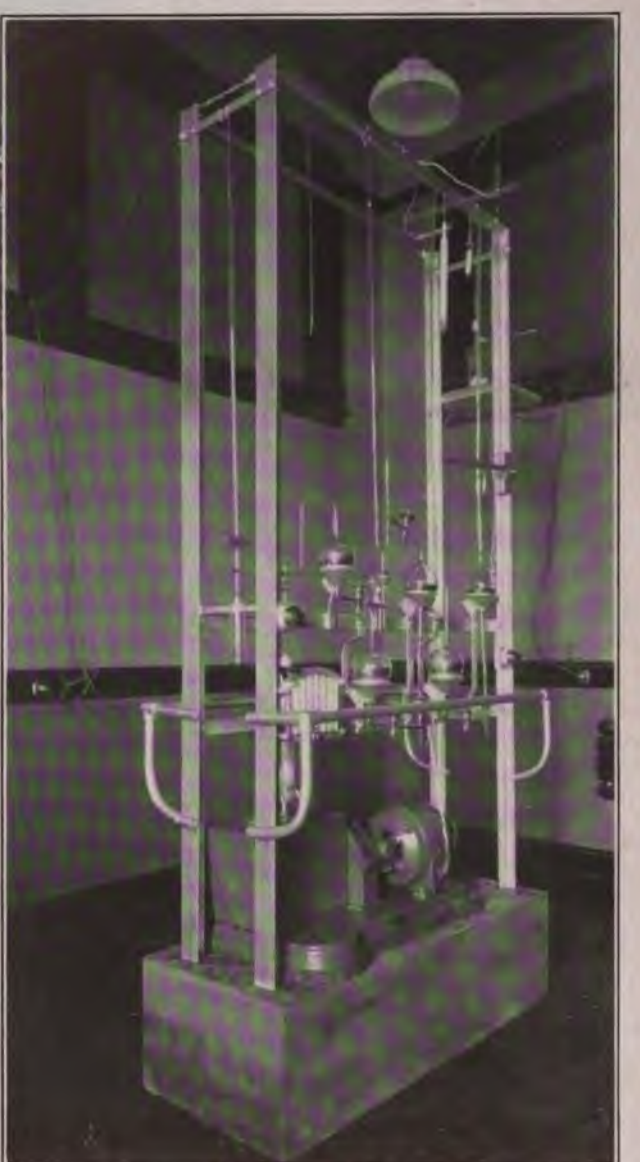

Fig. 1.—Photograph of Debierne-Duane-Failla apparatus. The photograph shows the single type of apparatus. The duplex type is usually installed so that either side of the system may be available in case of accident.

gen and oxygen to recombine. The purified emanation is then made to pass into vessel *12*, being finally compressed in the tube at cock *16*. It is then forced out into the capillary glass tube *18*. The distal portion

(1 or more cm., e. g.) of this tube containing the concentrated emanation is then cut off by a minute gas flame.

The mechanical details of the process are as follows: The auxiliary vacuum pump that is attached to vessel *25* is started and stopcocks *22* and *8* are opened in order to create a vacuum in the line *8-22* above the mercury in vessel *7*. Stopcock *6* is now opened and the mercury in *4* falls to the level in *7*. This allows the emanation, hydrogen, oxygen, ozone and water vapor to come out of the radium flask through tube *1* and to fill *4* by diffusion. Cock *22* is now turned to permit air to enter the line *8-22* through the drying tube *23* containing calcium chloride. This forces the mercury up in *4*, driving the gases ahead of it and past the

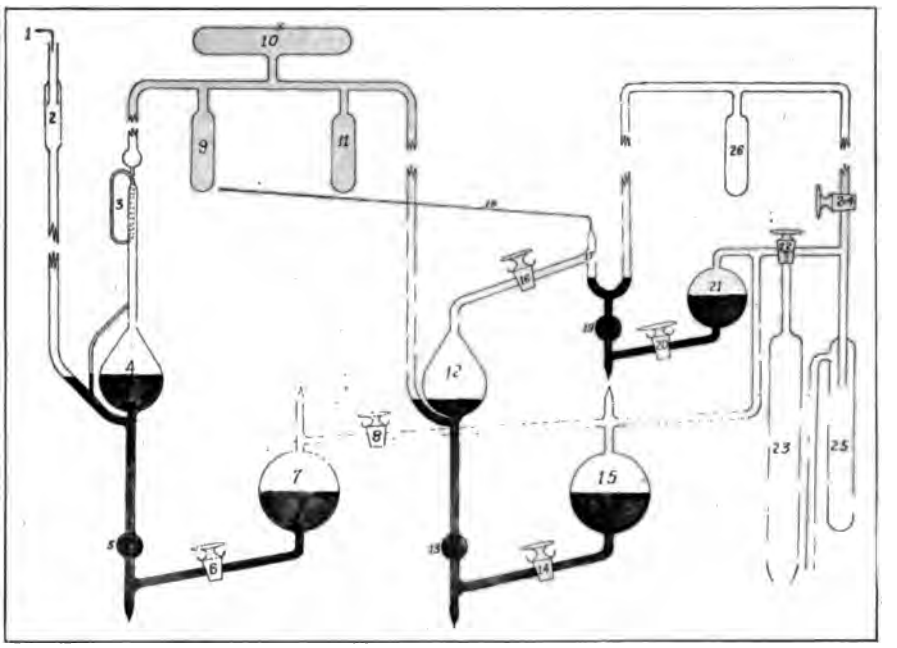

Fig. 2.—Diagrammatic plan of apparatus in Fig. 1.

trap *3* into the purification chamber (*9*, *10* and *11*). Cock *22* is again turned to connect the line *8-22* with the auxiliary pump and the mercury in *4* again falls, allowing another portion of the accumulated gases to fill the bulb. The mercury in trap *3* prevents the backward passage of gases from *9*, *10*, *11* to *4*. This procedure of filling *4* with the gases and forcing them up past the trap *3* into the purification chamber is repeated until all the gases are pumped over. The completion of the process is easily detected by the fact that when there is no gas present, the rising mercury in *4* produces a sharp metallic click when it strikes the mercury in trap *3*.

Before the pumping process just described is started, the purification chamber (*9*, *10* and *11*) is tested to insure the existence therein of a good

vacuum. If gases are found to be present, they are pumped through *16* and *17* into *26* by means of the mercury pump *12*, *13*, *14* and *15*. From there they may be exhausted into the room through *24* by the auxiliary pump and thence out of the room by means of a ventilating fan.

When a high vacuum has been established in the purification chamber, an electric current is sent through the copper oxide coil *10*, the strength of this current being just sufficient to bring the coil to a low dull-red heat. When the coil is hot, the purification chamber is ready to receive the gases from *1*. As they meet the hot coil, the hydrogen and oxygen reunite and form water which is immediately absorbed by the phosphorus pentoxide (P_2O_5) contained in *11*. By this action most of the gas entering the purification chamber is eliminated. If any carbon dioxide, chlorine or hydrogen chloride are present, they are absorbed by the sodium hydroxide in *9*. Thus by the time all the gases are pumped out of the radium flask into *9*, *10*, *11*, consuming, let us say one hour of time, there is little left in the purification chamber except helium and the radium emanation itself, all other gases having been absorbed.

The emanation is now ready to be pumped over into the capillary tube *18*. With the line *8-22* at atmospheric pressure, stopcock *20* is opened and the mercury is allowed to rise a few centimeters in the y-shaped tube above *19* to prevent communication between *17* and *26*. During the purification process the bulb *12* is left partly filled with mercury in order to prevent its being filled with the gases that are to be purified. With a vacuum in the line *8-22*, stopcock *14* is opened, the mercury falls in *12* and the emanation, expanding from the purification chamber, fills this bulb. Stopcock *22* is now turned to connect line *8-22* with atmospheric pressure. This causes the mercury to rise in *12* and as it nears the top of the bulb, stopcock *16* is opened and the emanation is forced out into *17* by running the mercury about 1 centimeter past *16*. Stopcocks *14* and *16* are then closed. Line *8-22* is again exhausted, stopcock *14* is reopened, and the mercury falls out of *12* which is again filled with emanation. In this manner practically all of the emanation may be pumped over into *17*.

When the mercury has been raised in *12* for the last time it is allowed to pass through *16* and up to *17*. The emanation is then forced by means of the mercury in *21*, by opening stopcock *20*, into the capillary tube *18*. The mercury rises in the capillary and when the desired concentration is effected, stopcock *20* is closed. The capillary glass tube is about 1 millimeter in diameter, and can be sealed off very readily by means of a small pin-hole gas flame. The part of the capillary tube sealed off containing all the emanation is then divided by means of the same flame into as many pieces as are desired. In this manner, any percentage of the total amount of emanation is obtained for use in a small tube, of, e.g., 1 centimeter length. These small glass tubes are then inserted into

TABLE V

SHOWING THE RISE OF GAMMA RAY ACTIVITY DUE TO RaC THROUGH 2 CM. OF LEAD

TIME:	ACTIVITY OF AN EMANATION TUBE MEASURED IN PERCENTAGE OF MAXIMUM VALUE:
0	0
2 min.	.025
5 "	.32
10 "	1.90
20 "	8.9
30 "	19.0
40 "	30.0
50 "	41.2
60 "	51.3
1 hr. 30 min.	74.4
2 "	87.8
2 " 30 min.	94.7
3 "	98.0
4 "	99.9

enameled silver tubes the ends of which are blocked with paraffine. They are then set aside for 3½ hours before their activity is measured. The next day the same procedure is repeated in order to withdraw and concentrate the emanation which has accumulated in the preceding 24 hours.

When the emanation is first admitted to the capillary tube its activity, measured by the penetrating rays, is zero. As the emanation decays,

TABLE VI

SHOWING THE RATE OF DECAY OF RADIUM EMANATION

TIME	PERCENTAGE OF MAXIMUM ACTIVITY (THEORETICAL)
0	100.00
1 hr.	99.25
2 hrs.	98.51
3 "	97.77
4 "	97.04
5 "	96.32
6 "	95.60
12 "	91.39
1 day	83.53
2 days	69.77
3 "	58.27
4 "	48.68
5 "	40.66
6 "	33.96
1 week	28.37
2 weeks	8.05
3 "	2.28
4 "	0.647
10 "	0.000337

however, the active products, Radium A, Radium B, and Radium C are formed, producing an invisible film on the walls of the tube. The penetrating radiations from these products gradually increase until the tube reaches its maximum activity. This takes place about 4 hours after the emanation has been sealed in the capillary glass tube. The growth of the activity of Radium C with time is shown in Table V.

About one hour after the maximum value of the gamma radiation has been reached, the activity of the tube begins to decay with the same "time period" as that of the emanation. In other words, 16 per cent of the activity is lost every 24 hours. The activity at any given time will be reduced to ½ the value at that time after 3.85 days have elapsed.

Table VII shows the calculated decay of radium emanation tubes from day to day. For example: Let us find the number 78 in the single left

TABLE VII

RADIUM EMANATION DECAY TABLE

1	1	2	3		1	2	3		1	2	3
90	75	63	52	60	50	42	35	30	25	21	17
89	74	62	52	59	49	41	34	29	24	20	17
88	74	61	51	58	48	40	34	28	23	20	16
87	73	61	51	57	48	40	33	27	23	19	16
86	72	60	50	56	47	39	33	26	22	18	15
85	71	59	50	55	46	38	32	25	21	17	15
84	70	59	49	54	45	38	31	24	20	17	14
83	69	58	48	53	44	37	31	23	19	16	13
82	69	57	48	52	43	36	30	22	18	15	13
81	68	57	47	51	43	36	30	21	18	15	12
80	67	56	47	50	42	35	29	20	17	14	12
79	66	55	46	49	41	34	29	19	16	13	11
78	65	54	45	48	40	34	28	18	15	13	10
77	64	54	45	47	39	33	27	17	14	12	10
76	64	53	44	46	38	32	27	16	13	11	9
75	63	52	44	45	38	31	26	15	13	10	9
74	62	52	43	44	37	31	26	14	12	10	8
73	61	51	43	43	36	30	25	13	11	9	8
72	60	50	42	42	35	29	24	12	10	8	7
71	59	50	41	41	34	29	24	11	9	8	6
70	59	49	41	40	33	28	23	10	8	7	6
69	58	48	40	39	33	27	23	9	8	6	5
68	57	47	40	38	32	27	22	8	7	6	5
67	56	47	39	37	31	26	22	7	6	5	4
66	55	46	38	36	30	25	21	6	5	4	3
65	54	45	38	35	29	24	20	5	4	3	3
64	53	45	37	34	28	24	20	4	3	3	2
63	53	44	37	33	27	23	19	3	3	2	2
62	52	43	36	32	27	23	19	2	2	1	1
61	51	43	36	31	26	22	18	1	1	1	0
60	50	42	35	30	25	21	17	0	0	0	0

hand vertical column. A tube having a strength of 78 mc. decays each twenty four hours as follows—66 mc., 54 mc., 45 mc., i.e., reading horizontally to the right. By finding 45 in the second single vertical column the values for the following three days are found to be 38 mc., 31 mc., 26 mc. By finding 26 in the third single vertical column the values of this tube for the following three days are found to be 22 mc., 18 mc., 15 mc., and so on.

MEASUREMENT OF THE GAMMA RAY ACTIVITY OF EMANATION TUBES

The measurement of the activity of the emanation tubes is made after they have reached their approximate maximum strength. The measurement is most easily and accurately done by means of the gold leaf electroscope. A diagram of this instrument is shown in Fig. 3.

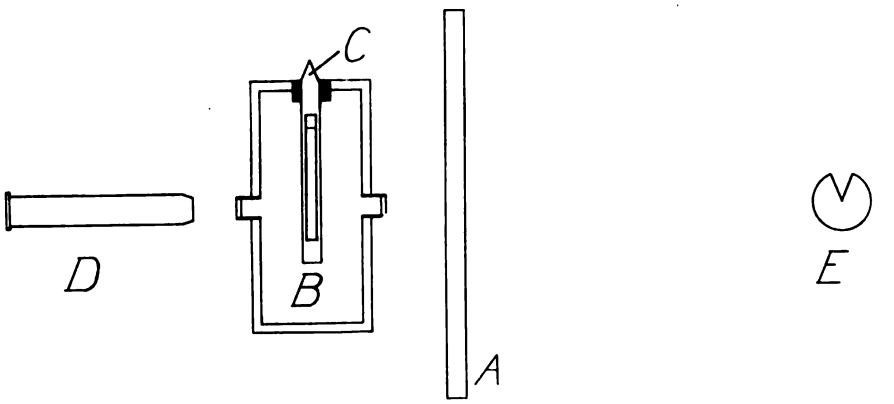

Fig. 3.—Diagram of electroscope.

A is a plate of lead 1 centimeter thick used to eliminate all of the easily absorbable rays. *B* is a metal box containing the gold leaf system. When the system is charged through *C*, e.g., with positive electricity, the gold leaf, which in the uncharged condition hangs vertically, is forced out into a partially horizontal position being thus brought into the field of the microscope, *D*.

In order to measure the quantity of a radioactive substance in a small capillary tube, the latter is placed in the V-shaped holder at *E*. The penetrating gamma rays then pass through the lead plate, *A*, into the electroscope, *B*, and the air in the electroscope is thus made a conductor of electricity. This is known as "ionizing" the air. In other words, the radium rays generate small positive and negative "ions" or charges of electricity in the air. If the gold leaf is charged positively, it will attract the negative charges to itself. The negative charges will thus neutralize a part of the positive charges of the leaf. The leaf will then tend to come

nearer into the uncharged or vertical position and will thus move across the field of the microscope. The rate of this motion is a measure of the number of "ions" formed per second in the air, and this in turn indicates the intensity of gamma or penetrating rays from the emanation tube. The larger the amount of emanation in the tube at *E*, the faster will be the movement of the gold leaf across the scale in the field of the microscope. The rate of motion of the leaf is ordinarily timed by means of a stop watch.

In order to facilitate the use of the electroscope in measuring unknown quantities of radium emanation, it is necessary to have at hand a standardized tube of radium. One then determines the rate of fall of the leaf in the electroscope caused by the known or standardized specimen. Mention may be made here of the International Radium Standard. This consists of 21.99 mg. of pure radium chloride containing 16.75 mg. radium element, which was prepared my Mme. Curie in 1910 at the request of the Brussels Congress of Radiology and Electricity. This was sealed in a glass tube and is kept at the International Bureau of Weights and Measures at Sevres, France. Other countries have standards as follows: Austria, 31.17 mg., England, 21.13 mg., Germany, 19.73 mg., Japan, 9.80 mg., Portugal, 9.09 mg., Sweden, 9.73 mg., United States, 20.18 mg.

The unit in which quantities of emanation are expressed is called the curie. This has been defined as the quantity of emanation in equilibrium with one gram of radium element. For practical purposes a smaller unit, the millicurie, $\frac{1}{1000}$ of a curie, is used. The gamma ray activity of a millicurie corresponds to the gamma ray activity of one milligram of radium element. The microcurie is $\frac{1}{1000}$ of a millicurie and corresponds to one microgram of radium element.

The number of milligrams of radium element in the "standardized" tube, divided by the number of millicuries of emanation in the unknown tube is equal to the ratio of the number of ions produced per second when the "standard" and the emanation tube are successively placed at *E*. This last ratio is equal to the inverse ratio of the time of fall of the gold leaf across the scale of the microscope. Therefore in order to measure an unknown quantity of emanation it is only necessary to obtain the relative rates of fall of the gold leaf when the "standard tube" is used and when the "capillary emanation tube" is used and multiply this ratio by the number of milligrams of radium element used as the "standard." If the activities of the standard and the emanation tube are of very different magnitudes, the natural leak of the electroscope must be taken into account in calculating the activity of the emanation.

If for any reason the error due to natural leak is not considered great enough to affect seriously the result, the following simple formula is used as a basis for the calculations involved.

$E = s\frac{a}{b}$ where
- E = activity of emanation tube.
- s = activity of standard.
- a = time of passage of leaf over any desired number of scale divisions under action of standard.
- b = time of passage over same number of scale divisions under action of emanation tube.

Let us suppose, for example, that we have as a "standard" a tube containing 15 milligrams of radium element (the activity being therefore equivalent to that of 15 millicuries), and an unknown emanation tube, the activity of which is to be measured. The "standard" is placed at any convenient distance from the electroscope and the latter is charged, so that the leaf diverges. The time of passage of the leaf, e. g. 40 divisions, is observed. Let us assume this elapsed time to be 1 minute (a). The emanation tube is now substituted for the "standard" and a similar observation taken. We will assume the time in this case to be 50 seconds (b). Substituting in the above formula the values of s, a and b which are now known we find $E = 15 \times \frac{60}{50} = 18$ mc.

It will be observed that, within certain limits, the distance of the "standard" and the emanation tube from the electroscope during the calculation is immaterial. The number of scale divisions, over which the reading is made, is likewise unimportant. But whatever the distance or number of scale divisions chosen, observance of the following precautions is vital to the securing of dependable results: (1) The standard and the emanation tube must, in turn, be placed at exactly the same distance from the electroscope.

(2) While readings are being made on one tube, the other tube should be placed 30 or 40 times as far away and preferably behind a heavy lead screen.

(3) The same number of scale divisions over the same region of the scale must be used in each reading. If, as has been suggested above, the rate of natural leak of the electroscope is sufficiently great to have an appreciable effect on the results, allowance for this must be made in the calculations. In this case the formula takes the form:

$$E = S\frac{a - \frac{ab}{c}}{b - \frac{ab}{c}}$$

Here c is the time taken by the leaf when no tube is present in passing over the number of scale divisions chosen for the readings. Let us suppose, as is the case in our laboratory, that this is of the order of 25 minutes; the formula then becomes:

$$\frac{ab}{c} = \frac{60 \times 50}{25 \times 60} = 2$$

$$E = 15 \times \frac{60 - 2}{50 - 2} = 18.13$$

This error (.13) (less than 1 per cent) for many purposes is negligible, at least in small tubes, and, as a rule, in cases similar to this the correction would not need to be made. But if the activity of the "standard" and the tube to be measured is not approximately the same, failure to make the correction would lead to a considerable error. For example, assuming *s*, *a* and *c* to have the same values as before, but assuming b = 10 seconds, then

$$E = 15 \times \frac{60}{10} = 90 \quad \text{(uncorrected)}$$

$$\frac{ab}{c} = \frac{60 \times 10}{25 \times 60} = .4$$

$$E = 15 \times \frac{60 - .4}{10 - .4} = 93.12$$

This would lead to an error of considerably over 3 per cent if the correction were not applied.

The Preparation of the Active Deposit.—As we have previously stated, it is sometimes desired to collect a quantity of active deposit on a sheet of metal foil. In order to accomplish this, a piece of lead foil of about 0.1 mm. thickness is rolled in such a way as to fit snugly into a glass tube, closed at one end. This tube, containing the foil, is then sealed in a vertical position, to the emanation apparatus at 17 instead of the usual capillary tube. (See Fig. 2). After the air has been pumped out, the purified emanation is forced into the tube by means of mercury raised to the lead foil. After 3 or 4 hours, when the maximum amount of active deposit has been formed and deposited on the foil, the mercury is lowered and the emanation allowed to pass into another part of the apparatus to be collected in the usual manner. When the tube is cut off and the foil carefully removed, its activity may be measured by means of a gamma ray instrument. As in the case of the emanation, the unit of quantity is the millicurie. This foil may be used as a uniform source of radiation of short duration.

When a radioactive solution is required for injection into the blood, it may be prepared in the following manner: A small amount of common salt (NaCl) is packed into a small glass bulb. This bulb is heated in a gas flame in order to thoroughly dry the salt, and is then sealed to the emanation apparatus at *17* (see Fig. 2) just as in the preparation of active deposit on the lead foil. After the air is pumped out, the purified

emanation is forced into the salt, by means of mercury raised to the small bulb. In 3 or 4 hours, when the maximum amount of active deposit has formed and collected on the salt grains, the mercury is lowered again. The emanation is allowed to pass into another part of the apparatus to be collected in the usual way. The bulb is then cut off and distilled water is forced in with a hypodermic syringe in sufficient amount to make approximately a normal physiological salt solution. The "active" water is subsequently withdrawn in the syringe.

As in the former case, the amount of active deposit in the syringe is determined by the gamma-ray instrument. The activity of the syringe is usually determined before and after the injection of the solution, in order to estimate the exact quantity of active deposit administered. The quantity administered will be the difference in these 2 values. Proper allowance for the decay of the active deposit must be made.

CHAPTER V

THE RADIATIONS FROM RADIUM AND ITS DECAY PRODUCTS

Rutherford states that from a theoretical standpoint it is desirable to restrict the term "radioactive" to substances that undergo spontaneous atomic transformation. From this point of view, a few substances may be said to be radioactive which apparently emit no radiations at all but which do transform themselves spontaneously and give rise to new substances. From our present standpoint, however, we may fairly define a radioactive substance as one that, while undergoing atomic transformation, spontaneously and continuously emits peculiar rays. These rays are invisible but are known to be present because of certain phenomena which they cause. Among the interesting properties possessed by these radioactive rays are their power to ionize a gas, to affect a photographic plate similarly to the actinic rays of sun light, to cause certain substances to fluoresce in the dark, and, most important of all, from our present standpoint, to cause the modification or destruction of vital tissues exposed to their influence. While radium itself emits the easily absorbed alpha rays, its decay products, Ra B and Ra C emit the more penetrating beta and gamma rays. The beta and gamma rays from Ra B are less penetrating than those from Ra C. Confined in a tube for therapeutic use, the only real function of radium or its next decay product, radium emanation, is to produce Radium A, B, and C as fast as the latter products disintegrate.

ALPHA, BETA, AND GAMMA RAYS

There are three different kinds of radiations emitted by the radioactive substances. These are known as alpha, beta, and gamma rays. The table previously given (see list of radioactive substances) will suffice to make clear the particular ray that each of the products emits.

It will be helpful to describe at this point the properties of the different kinds of rays.

Alpha Rays

Alpha rays are material particles having a double positive charge and a mass four times that of the hydrogen atom. In fact, they are merely positively charged helium atoms shot out from the radium atom, as it transmutes, with an initial velocity of 9,000 to 12,000 miles per second. They have a very great ionizing power, but are readily absorbed, the thinnest layer of metal or a sheet of note paper being sufficient to stop them. The "range" or greatest distance that an alpha particle from any

of the radioactive substances can travel in air, depends upon its initial velocity and the temperature and pressure of the air. For an alpha particle of radium in air at standard conditions of temperature and pressure, the range is 3.3 cm. In other words, the alpha rays of radium are completely absorbed or stopped by 3.3 cm. of air and beyond this distance their characteristic effects cannot be detected. Alpha rays are analogous to the canal rays of a Crookes tube, and like them may be deflected slightly by a very powerful magnetic field. While usually referred to as alpha rays, the term alpha particle is perhaps preferable.

A gram of radium in equilibrium with its decay products, Ra Emanation, Ra A, B, and C, emits energy with its rays at the rate of 136 calories per hour. Of this energy 125 calories are borne by the alpha rays, 4.5 calories by the beta rays and 6.5 calories by the gamma rays.

Beta Rays

Beta rays are swiftly moving, negatively charged electrons and are identical in type with the negatively charged particles constituting the cathode rays of the Crookes tube. They are about $1/1840$ the mass of the hydrogen atom. Soft, medium and hard beta particles may be distinguished according to their velocity and power of penetration. The slowest beta particles are comparable to alpha rays in penetrating power and are known as soft beta rays. The swiftest beta particles have about the velocity of light and have one hundred times the penetrating power of alpha rays. These are known as hard beta rays. The velocity of the hard beta rays from Ra C is 96 per cent of the velocity of light and it is estimated that to give an electron this initial velocity requires a difference of potential of 2,000,000 volts (approximately a 16 foot spark in air). Between the softest and hardest beta rays there is a series of so-called medium beta rays, which are intermediate in their power of penetration. The beta rays derived from Radium B and Radium C are one half absorbed after passing through 55 cm. of air at atmospheric pressure and room temperature. The beta rays from Radium C are half absorbed by 170 cm. of air. Beta rays may also be deviated in a magnetic field but in an opposite direction to the deviation of the alpha rays because the beta ray is the negative electron. Beta rays are also deflected much more than alpha rays because their mass is very much less than that of the latter. As we have previously mentioned in the case of the "alpha rays," the term "beta particle" is preferable. In deference to custom, however, the term "beta ray" is retained.

Gamma Rays

These are undulations of the ether, or electro-magnetic waves, and are similar to x-rays, except that their wave length is much shorter than that of the latter. The velocity of the gamma rays is the same as that of light.

The production of gamma rays is due to the very intense electronic vibrations which are set up in the structure of a radio atom from which a high speed beta ray is escaping. The forced vibrations of the electrons give rise to very high frequency or short wave length electro-magnetic waves or gamma rays. Thus it is seen that the gamma ray is a secondary phenomenon, and the energy of the gamma rays represents energy lost by the beta ray as it escapes from the atom which gives it origin. The absorption of gamma rays is an electronic property of matter, as contrasted with atomic or molecular absorption of longer wave lengths such as ultra violet and visible light. When the gamma ray pulse encounters an electron in matter which can vibrate in harmony, energy is transferred to the electron and it thereby takes up a high velocity and becomes a "secondary beta ray." This phenomenon of energy transfer from a wave to a particle has a very good analogy which is familiar to most of us in the sound vibrations which the striking of a certain note on an instrument will set up in a loose bit of woodwork, etc., in a music room. Here the energy borne on air waves is transferred to the particle which can vibrate in harmony with the rate of the air waves. In the case of gamma rays, so few electrons are encountered that can vibrate in harmony, that the gamma ray pulse must pass through enormous numbers of electrons, (i.e., great masses of matter) before it loses much energy. This interpretation explains the "hardness" or penetration of the gamma rays. In the case of x-rays, which have a much lower rate of vibration, more electrons are encountered that can vibrate in harmony; therefore the x-ray pulse loses its energy more easily, or, as we say, is more easily absorbed in matter.

The terms soft, medium and hard gamma rays are used to indicate different degrees of penetrating power, just as in the case of the beta rays. In general, gamma rays are from ten to one hundred times more penetrating than beta rays, and consequently have a smaller ionizing power. The gamma rays are half absorbed after passing through one hundred and fifteen meters of air. Like the x-rays, the gamma rays cannot be deflected by a magnet.

CHAPTER VI

ABSORPTION AND FILTRATION OF RAYS

We have already referred to the fact that the radiations are capable of penetrating opaque matter in varying degrees, certain types of rays being easily absorbed while other types are stopped with the greatest difficulty. In this chapter we shall consider some of the practical advantages of filtering or absorbing certain types of rays by means of screens.

ABSORPTION OF RAYS

Alpha Rays

It has already been stated that the alpha rays from radium are very easily absorbed. The glass wall of the emanation tube, a sheet of note paper, the film of a soap bubble or a layer of moisture on the skin is sufficient to stop them.

Beta Rays

Hard beta rays according to Rutherford may be half absorbed by 0.1 mm. and may be completely absorbed by 2 mm. of lead. The absorption of the beta rays by various kinds of matter follows closely an exponential law.

For example, if one half of a given quantity of beta rays of a certain type is absorbed by 0.2 cm. of aluminum, ¼ of the original amount of rays will be unabsorbed after passing through 0.4 cm. of aluminum, ⅛ of the original amount will be unabsorbed after passing through 0.6 cm., and so on until complete absorption. As we have stated before, the beta rays are heterogenous and have different penetrating powers. The relative absorption of beta rays depends therefore upon the type of rays that is chosen for experiment. The hardest or most penetrating beta rays are absorbed to the extent of 93.8 per cent by 1 cm. of epithelial tissue. Their intensity after passing through 1 cm. of epithelial tissue, is, therefore, only 6.2 per cent of that exhibited at the surface of the skin. This estimation does not take into account the diminution of intensity due to divergence of the rays with distance from the source. The intensity of the beta radiations from radium C is reduced to ½ the initial intensity after passing through 17 meters of air, at ordinary room temperature and atmospheric pressure.

Gamma Rays

The hard gamma rays from radium C are half absorbed by 14 mm. of lead. Just as in the case of the beta rays, the gamma rays from radium

are absorbed approximately in accordance with an exponential law. This law is followed, however, only in the event of the rays being allowed to pass first through a few millimeters of lead, the softer gamma rays being thus absorbed.

According to the measurements of Giraud, which have been mentioned previously 20.4 cm. of water will absorb ½ of the gamma rays from radium. For theoretical purposes, water may be considered as the equivalent of soft tissues in absorbing power.

Gudzent states that 4 per cent of the successively remaining gamma rays are absorbed by each centimeter of tissue traversed.

According to Rutherford 26.5 cm. of soft tissue would be required for the half absorption of the hardest gamma rays from radium.

These estimations may be compared with the penetrating power of x-rays which are half absorbed, according to Colwell and Russ, by 4.9 cm. of soft tissues. As to the diminution of their intensity with distance, hard gamma rays are reduced to one half their initial intensity after passing through 115 meters of air at ordinary conditions of room temperature and atmospheric pressure.

Secondary Radiations

All three types of rays—alpha, beta and gamma—produce secondary radiations when they impinge upon matter. We may briefly consider the secondary radiations produced by each of the three types of rays.

(a) The secondary rays produced by the alpha rays are slow beta particles and are sometimes called "delta rays." The secondary rays due to alpha rays are naturally without practical importance from the therapeutic standpoint. (b) Just as the cathode rays, striking the target of the x-ray tube, set up x-rays, so the primary beta rays from radium when they strike matter set up a type of gamma radiation. The intensity and penetrating power of these secondary gamma rays increase greatly as the atomic weight of the substance impinged upon increases, since these gamma rays correspond to the characteristic x-rays for the particular element, and the higher the atomic weight of the element, the more penetrating are the characteristic x-rays. The quantity of secondary gamma rays that are produced depends upon the amount of beta radiation that is absorbed and the thickness of the material that is radiated. (c) When the primary gamma rays from radium strike matter, a part of the original beam is scattered in all directions although the quality of the beam is not altered. Just as in the case of the primary beta rays secondary radiations are also set up by the primary gamma rays. These consist of secondary gamma rays and secondary rays of the beta ray type. Our knowledge of the secondary gamma rays is very imperfect. The secondary beta rays have a penetrating power that is nearly equivalent to that of the primary beta rays. When heavy elements such as lead

are impinged upon by gamma rays the secondary beta radiation is somewhat more penetrating than when lighter elements such as brass or aluminum are radiated.

FILTRATION OF RAYS

The principle of filtration and the use of screens in the treatment of diseased tissue may be referred to at this point. Wickham, Degrais and Dominici were apparently the first to use and advocate the employment of rays obtained by filtration. By interposing between the radioactive substance and the tissue to be treated, various metallic and nonmetallic materials, the less penetrating rays may be absorbed, i.e., removed by filtration. Substances used for absorbing radiations are known as screens or filters. In the treatment, for example, of a tumor below the surface of the skin, we may absorb by means of screens the undesirable types of rays before they reach the skin, allowing only the more penetrating rays to pass through the screen and affect the tissues. The skin, being thus relieved of the absorption of the less penetrating rays, will receive a minimum amount of injury, while the deeper layers of tissue under proper conditions, may receive nearly as much radiation as the superficial layers.

If we wish to absorb the alpha rays we may theoretically place between the radium and the skin a screen of $\frac{1}{100}$ millimeter of aluminum or a sheet of writing paper. In reality, however, the alpha rays do not penetrate the walls of the glass tube or other apparatus in which the radium is confined.

If we wish to intercept most of the beta rays we may interpose between the radium and the tissues a screen of 1 millimeter of lead. This filters out more than 99 per cent of the beta rays. One may thus use nearly pure gamma rays, which will not be absorbed but will pass through the screen. When massive doses of deeply penetrating rays are used, it is desirable to absorb in addition part of the softer gamma rays. Brass screens 2 mm. thick may then be used. It is quite evident that a whole series of metallic screens of different thicknesses and densities may be used in order to absorb or filter out varying portions of the beta and gamma rays and that the results of treatment will vary accordingly.

Screens

The screens used for all types of therapeutic applicators may be described here. Screens are ordinarily made of silver, gold, platinum, brass, lead or aluminum. For external applications, brass or silver screens answer almost every purpose. It is believed that the secondary radiations from brass are not so irritating as those from denser metals. It is best to use rather simple and uniform screening until familiarity is obtained with the effects of radium on the tissues.

When treating the interior of the various natural cavities of the body, such as the uterus, esophagus, etc., gold or platinum screens have a certain advantage as their great density permits the use of a much thinner screen than if brass or silver were used. In such case the desirable effect of distance in reducing the intensity of the rays is sacrificed. This may be compensated at times by the use of thicker nonmetallic coverings such as rubber of 2 or 3 mm. thickness. While theoretically screens of almost any material or thickness may be employed, it is often advisable in actual practice to employ a few different thicknesses of the same metal in order to simplify the technic. Silver screens having a thickness of 0.1 mm., 0.5 mm., 1 mm., and 2 mm. are probably the most generally useful in the routine application of radium. Screens of these thicknesses will absorb approximately 50 per cent, 96 per cent, 99 per cent, and 100 per cent of the beta rays. The skilled technician may use a greater variety of screens. In addition to those already mentioned the following screens are useful.

Lead ..... 1/10, 5/10, 1, and 2 mm. thick.
Platinum ..... 3/10 and 5/10 mm. thick.
Aluminum ..... 1/100, 5/100, 1/10 mm. thick.
Brass ..... 5/10, 1, 2, 2.5 mm. thick.

For practical purposes it is sufficiently accurate to say that the absorbing power of a metal for a given type of beta or gamma ray increases in proportion to its density.

Table VIII will suffice to indicate the relative density and consequent ray-absorbing power of various materials, some of which are used as screens.

From a consideration of this table it is an easy matter to calculate the thickness of different materials which would be required to absorb

TABLE VIII

RAY ABSORBING SUBSTANCE:	DENSITY (APPROXIMATE)	THICKNESS REQUIRED TO ABSORB 50% OF THE HARD BETA RAYS	THICKNESS REQUIRED TO ABSORB 99.9% OF THE HARD BETA RAYS
Gum rubber	1.0	1.00 mm.	8.50 mm.
Water	1.0	1.00 "	8.50 "
Soft tissues	1.0	1.00 "	8.50 "
Bone	1.7–2.0	0.60 "	5.00 "
Common glass	2.6	0.40 "	3.30 "
Aluminum	2.7	0.40 "	3.20 "
Steel	7.7	0.14 "	1.15 "
Brass	8.5	0.13 "	1.10 "
Nickel	8.7	0.13 "	1.10 "
Silver	10.6	0.10 "	0.80 "
Lead	11.3	0.10 "	0.80 "
Gold	19.3	0.06 "	0.50 "
Platinum	21.5	0.05 "	0.40 "

a given amount of the hard beta rays. Let us suppose, e.g., that we wish to use a series of brass screens which would equal $\frac{1}{10}$ mm., $\frac{5}{10}$ mm., 1 mm., and 2 mm., of silver. A simple calculation of the relative density of the metals shows that brass screens equivalent to silver screens of the above thicknesses, must be $\frac{10.6}{8.5}$ of $\frac{1}{10}$ mm., $\frac{5}{10}$ mm., 1 mm., and 2 mm.: i.e., approximately $\frac{1}{8}$ mm., $\frac{5}{8}$ mm., 1.25 mm., and 2.5 mm. thick. Similar calculations may be made for other materials in the table.

It has been found that different thicknesses of silver will absorb the proportions of the hard beta rays indicated in Table IX.

TABLE IX

THICKNESS OF SILVER SCREEN	PER CENT OF HARD BETA RAYS ABSORBED	PER CENT OF HARD BETA RAYS LEFT
0.1 mm.	50.	50.
0.2 "	75.	25.
0.3 "	87.50	12.50
0.4 "	93.75	6.25
0.5 "	96.88	3.12
0.6 "	98.44	1.56
0.7 "	99.22	0.78
0.8 "	99.61	0.39
0.9 "	99.81	0.19
1.0 "	99.91	0.09

Upon examining the table it may be seen that the percentage of absorption by a given thickness of the metal follows an exponential law; i.e., if 50 per cent of the hard beta rays remain unabsorbed after passing through 0.1 mm. of silver, $\frac{1}{4}$ of the original amount will remain unabsorbed after passing through 0.2 mm., $\frac{1}{8}$ of the original amount will remain unabsorbed after passing through 0.3 mm., and so on until its complete absorption.

Depending upon the apparatus with which they are to be used and the lesions that are to be treated, screens of different shapes and sizes may be required. For the glazed plaques, pieces of metal of the material and thickness desired may be cut to fit the face of the apparatus. The metal screens may be round or square or of any other shape desired. While they may be made extemporaneously, it is much more convenient to use screens that have been previously fitted to suit each apparatus.

For the tubes containing radium or radium emanation, a set of cylindrical metal screens of different patterns is also essential. It is convenient to have certain screens made in such a way that part of the wall is cut out to form a window ("window screen"). One may thus treat a certain part of a lesion opposite the window with a greater volume of rays than the other parts.

Secondary Radiations

In the practical use of screens or filters we meet with difficulties on account of the secondary radiations (Rays of Sagnac) that are formed in these screens. As these secondary radiations are less penetrating than the primary radiations that produce them they always tend to defeat the object of the screen. While the secondary radiations may not seriously affect the skin surface, it is customary, as we have said before, to interpose between the metallic screen and the skin, one or more millimeters of nonmetallic substance, such as gauze, rubber, filter paper, or wood, in order to absorb them. Filter paper is excellent and, being composed of pure cellulose of low density, does not appreciably absorb the gamma rays. Cork or soft wood is commonly used by the writer because of its greater convenience. According to Hayward Pinch, a layer of aluminum 0.2 mm. in thickness completely absorbs these secondary "rays of Sagnac."

CHAPTER VII

THE ABSORPTION OF GAMMA RAYS IN WATER

In this chapter we shall give the results of some of our experimental work on the absorption of gamma rays.

In these experiments, which were undertaken primarily to determine, if possible, the absorption of gamma rays in tissues, it was, of course, impossible to place the ionization chamber used in determining the intensity of the radiations beneath the skin itself.

Water was therefore used in our experiments as being the most suitable medium, inasmuch as it is similar in absorbing properties to the tissues. This medium was previously employed by Kroenig and Friedrich for determining the absorption of x-rays.

The main problem that we undertook to solve was whether the scattering of the gamma rays causes any change in the intensity of the rays at various depths below the surface of the skin and if so what the change is.

So far as the physical side of the problem of absorption and scattering of radiations is concerned, almost all the previous work mentioned in the literature has been done by simply interposing thin sheets of absorbing material between the source of radiation and the electroscope. In some cases an ionization chamber was used. Of such nature, for example, was the work of Hewlett, who discusses the mass absorption and mass scattering coefficients of radiations of wave length .13 to 1.05 A° in various substances including water. He found the mass absorption coefficient by finding the ratio of the filtered to the unfiltered beam. The results indicated excess scattering for the shorter wave lengths.

Kovarik treats of the effect of different types of ionization chambers. He used an amplification of the current with a three electrode tube.

Christen treats the problem of measuring "intensity" and "dose" from a theoretic standpoint. Kroenig says that the capacity can be made low by using a very fine center electrode, but if this is done, the saturation voltage is high.

Kroenig and Friedrich, in their work "Physikalische und Biologische Grundlagen der Strahlen-therapie," deal extensively with x-ray measurements of this nature. We may, therefore, give some of the details of their experiments. In his experiments with x-rays Friedrich used an apparatus of practically the same form as the first type of chamber which we employed; the only difference consisted in the fact that in his apparatus the connecting tubes were much larger and were insulated with rubber. The method that he employed has the great advantage of being flexible

but the insulation probably could not have been as satisfactory as in our apparatus. The size of the cable gives it a smaller capacity, but may render the scattering different.

Friedrich used a Wulf string electrometer, which has a very small capacity but is very insensitive. In fact, he found it impossible even to calibrate his apparatus with seventy milligrams of radium, because the other errors due to leaks were so large. He was forced to use a gram of radium and even under these circumstances did not take data under water.

For almost all of his measurements of gamma rays Friedrich used only an electroscope, not an ionization chamber. His apparatus was placed on a wooden table in the middle of a room in order to avoid "scattering."

Friedrich also had trouble with polarization of the dielectric; i.e.,

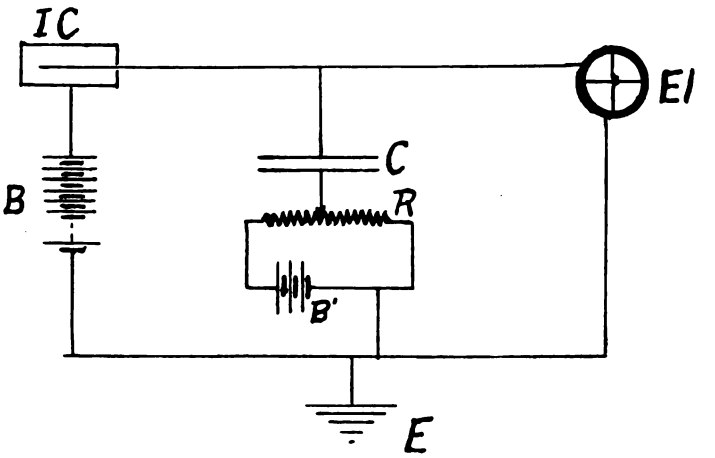

Fig. 4.—Diagram showing electrical connections for null method of using ionization chamber. *El*, electrometer or electroscope; *R*, rheostat; *IC*, ionization chamber; *E*, earth; *C*, condenser; *B*, *B'*, batteries.

charges crept out of it as one first used it; this had also been observed with our own apparatus which we shall describe below.

Friedrich constructed an ionization chamber of aluminum having found that this material was the one of the lowest atomic weight that was best suited for his purpose. He also constructed a chamber made of horn coated with graphite. He used carbon for the electrodes. Friedrich calibrated his aluminum chamber with the horn chamber for comparison of different hardnesses of x-rays.

Makower and Geiger ("Practical Measurements in Radioactivity") give a null method of using an ionization chamber. This method consists in balancing the current to be measured (in the ionization chamber) with the charge induced on a condenser, arranged in the manner shown, by varying the voltage applied to the other plate of the latter. (Fig. 4.) The principle of the apparatus consists in keeping the gold leaf

or mirror as nearly stationary as possible by moving the variable contact on the rheostat, and in measuring the time necessary for a given amount of motion of the latter.

There appeared to us to be but two methods open for experimentation if we were to be successful in measuring the gamma ray intensity of radium beneath the surface of water. By one method it was possible for us to put the electroscope itself under the water; by the other method we could use an auxiliary chamber which could be connected in some manner with the electroscope. The first method involves making a water-tight electroscope with an insulated and leak-proof connection to the outside for charging. It also requires that observations be made through the water with the consequent necessity of bringing the observing telescope and support near to the point at which the intensity is to be measured. The latter point seems important although the scattered radiation must follow the inverse square law; hence the amount of radiation reaching the electroscope would be approximately proportional to the inverse fourth power of the distance from the source under the conditions assumed.

The second method consists in placing an ionization chamber at the

Fig. 5.—Diagram of first type of ionization chamber. *al*, aluminum; *s-s*, sulphur; *i-e*, inner electrode; *g.t.*, guard tube.

point at which the intensity is to be measured. The chamber may then be connected with an electroscope which is thus in an easily accessible position.

The second method was chosen as being most suitable for our purpose.

A water-tight ionization chamber, 3 cm. long, 1.56 cm. in interior diameter, with walls .8 mm. thick was constructed of aluminum (Fig. 5). The inner electrode was made of No. 22 aluminum wire, insulated from the chamber walls and guard tube with sulphur. The guard tube running from the chamber had an interior diameter of 6 mm. and was filled with sulphur. The other end of the chamber was closed with an aluminum plate. The length of the wire electrode inside the chamber was about 2.5 cm.

In addition, a water-tight box 55 cm. square and 35 cm. high was constructed (Fig 6). The ionization chamber was placed in the center of the box and about 15 cm. from the bottom, with the guard tube extending out through one side.

A wooden support for the radium applicator, that was capable of movement, was constructed so that the shelf for holding the radium to

be used could either be brought down to touch the ionization chamber or could be raised to a height of 25 cm. above it. The shelf could also be moved 25 cm. to the side in either direction. We thus obtained for the shelf a freedom of vertical motion amounting to 25 cm.; of sidewise motion 50 cm. in two directions. Later a string was found sufficient for changing the position of the radium and was therefore used to suspend the apparatus at different heights.

The level of the water and also the height of the radium applicator above the surface of the water could thus be varied. The ionization chamber itself was fixed.

The ionization chamber was first tested. A wire about four meters long covered with cotton insulation ran from the inner electrode, (connecting with the wire passing through the guard tube) to an ordinary gold leaf electroscope. With this arrangement the speed of leak was found to be extremely large and also variable. One seventh of a milligram of radium was sufficient to produce a considerable change in the

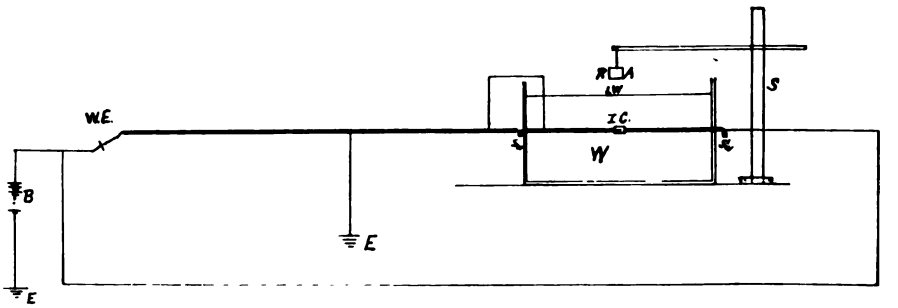

Fig. 6. – Diagram of apparatus used for measuring absorption of gamma rays in water. *W.E.*, Wilson tilted electroscope; *E*, ground; *B*, source of high potential; *Sw*, *Sw'*, switches; *W*, water; *I.W*, level of water; *R.A.* radium applicator; *S*, adjustable support; *I.C.*, ionization chamber.

leak, but, of course, the actual current in the chamber itself was entirely too small to be measured.

The use of sulphur supports which were encased in glass for the wire, did not materially lessen the size and variability of the leak. The wire was therefore encased in aluminum tubing filled with sulphur.

The first microscope used was of low magnification; hence the readings correspond to a large change in voltage.

It was found that the electroscope could be placed much closer to the radium than had been expected without introducing a leak due to the ionization in the electroscope comparable with the other leaks in the apparatus. A switch was introduced to separate the ionization chamber and the tube from the remaining parts of the conductor.

The switch that we used consisted of a very small glass cup imbedded in sulphur and filled with mercury, into which the wires dipped.

First Observations of Intensities With First Type of Ionization Chamber

Readings were taken with a very high potential on the leaf. The speeds of fall with the switch closed compared to those with the switch open varied almost inversely as the capacities of the two systems, thus showing that the reading was almost all leak and that there was little if any true current.

Readings were extremely irregular. It made a great difference how high the leaf was charged to start with; the leaf had to be kept charged for some time before taking readings; movements of the air affected results, etc.

The leak was minimized by using various devices until finally it was of the order of five minutes under very favorable conditions. Complete confidence could not be placed in the results of the readings, however. A voltage of about 430 volts, of which the scale corresponded to 25 or 30, was then used. The natural leak with radium present was still greater than the effect to be measured.

To get rid of this leak, an entirely different ionization chamber (Fig. 7) that could be used with a Wilson tilted electroscope was finally de-

Fig. 7.—Diagram of second type of ionization chamber. *S*, sulphur; *AL*, aluminum; *A*, amber.

vised. The inner chamber was made with approximately the same external dimensions as the previous chamber but heavy aluminum 3 mm. thick was used in its construction. The whole space between the inner and outer cylinders was filled with sulphur, except for the end at which the innermost electrode entered; this end was fitted with an amber washer. The guard tubes extending from each end were filled with sulphur as in the first type of chamber.

The advantages of this second type of chamber are evident. In the first place, the walls of the interior chamber can be charged to a high potential and the rise of the potential of the inner electrode from the ground potential up can be obtained. Under these circumstances, the only leak that can possibly occur in this part of the apparatus is from the inner electrode and the connecting wires to the ground. There can be no leak over the sulphur from high potential to the inner electrode because that is prevented by the guard ring. The current that may flow from high potential to the ground does not affect the electroscope. The only other leak possible is in the electroscope itself from the high potential to the leaf. The high potential difference is thus effective in producing the desired current, but only the low difference is effective in producing leaks.

This second type of chamber is also particularly suited for work with

the Wilson tilted electroscope, since the latter measures the rise in potential above that of the ground. The Wilson type of electroscope has the advantage of great sensitiveness; indeed the sensitiveness is very great if the electroscope is properly adjusted. Instead of the thirty or forty volt change in potential used with the ordinary electroscope, a voltage change of three or four volts or less can be used. Furthermore it has a low capacity; and the volume of gas contained is small.

Second Series of Observations with First Type of Ionization Chamber

An attempt was now made with the old chamber to apply the method which we proposed to use with the new chamber; i.e., the outer case

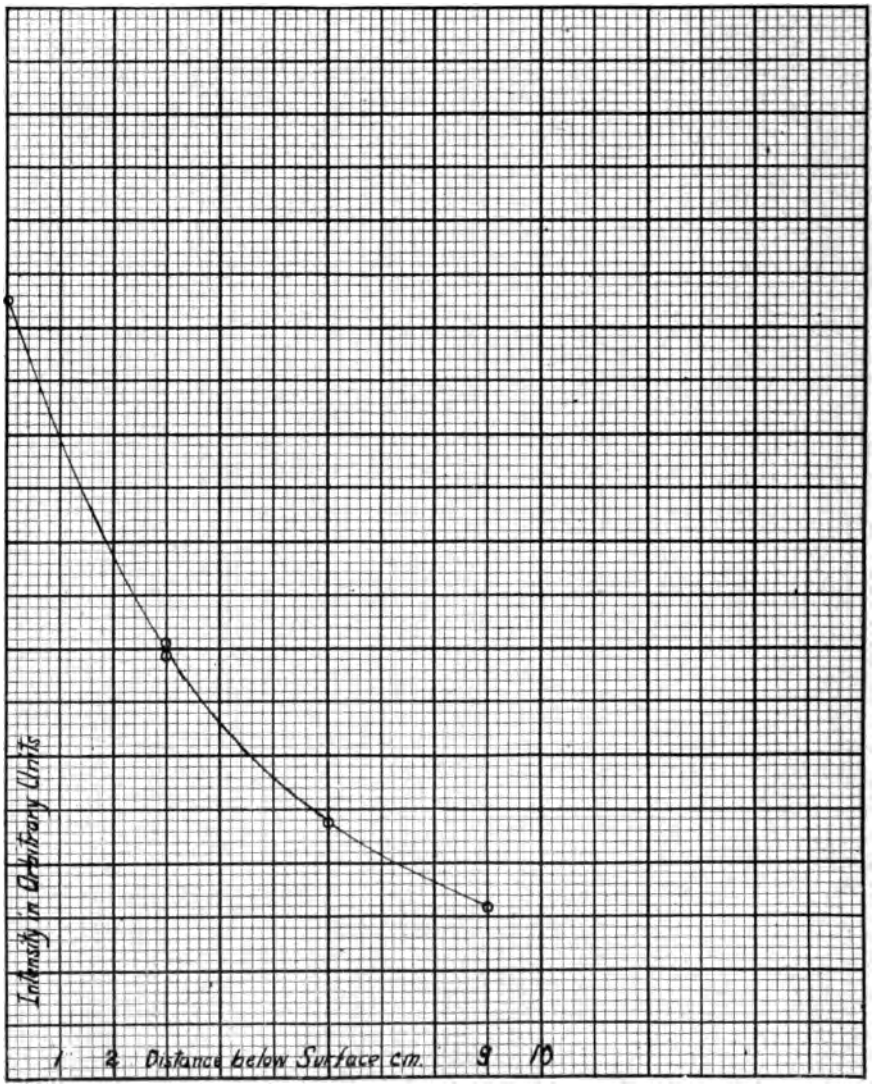

Fig. 8.--Intensity in water. Base of applicator 3 cm. above surface.

of the chamber was kept at high potential and the rise of the potential of the inner electrodes and leaf was noted. Unfortunately the results were not entirely trustworthy. The difficulty with the application lay in the fact that the guard tube for a distance of about twenty centimeters was necessarily at high potential, giving considerable opportunity for leaks across the end. However, the following results are at least qualitative as they indicate the manner in which the field in air, and at different distances below the surface of the water, varies.

Fig. 8 indicates that the intensity below the surface of the water nowhere approaches that at the surface, but decreases quite rapidly as one goes down. This is obviously to be expected, merely from the opera-

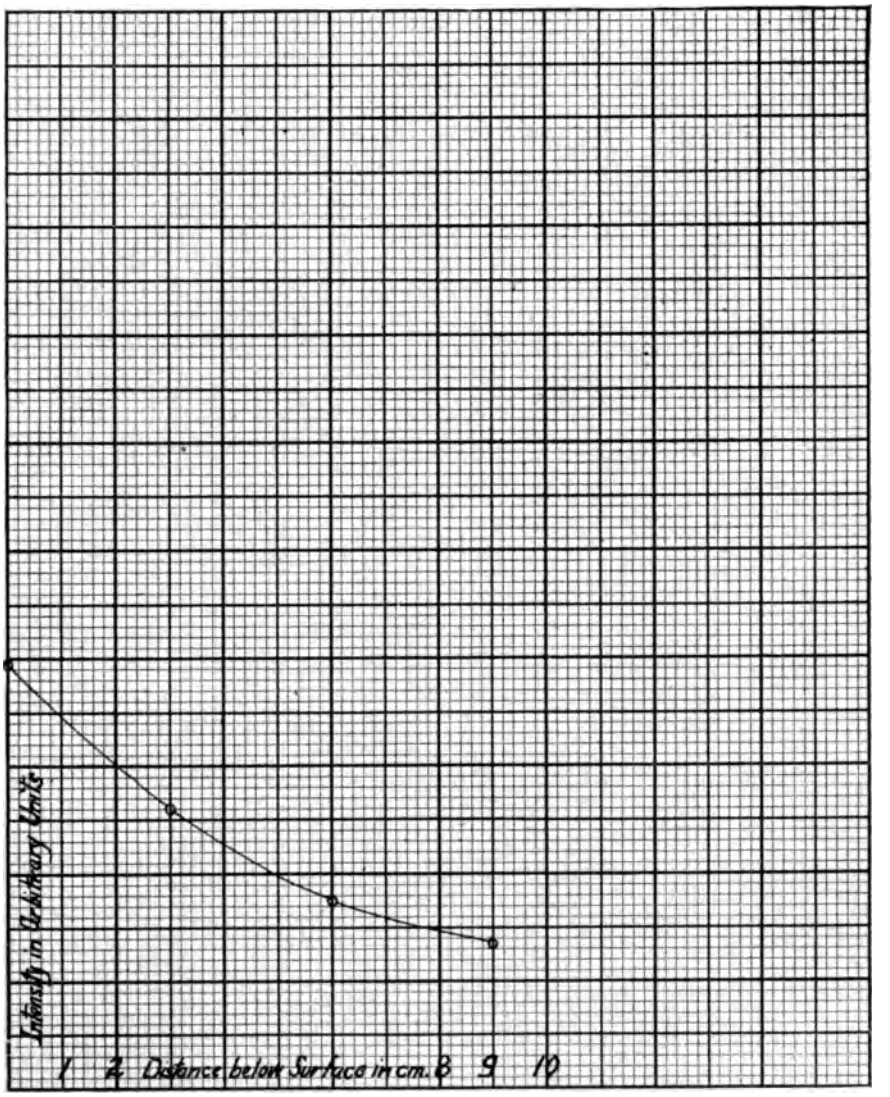

Fig. 9.—Intensity below surface of water. Base of applicator 6 cm. above water.

tion of the inverse square law alone. The curve is taken with the base of the applicator directly over the spot at which the field was measured, and at a constant distance of three centimeters from the surface of the water. It gives the intensity at various depths below the surface of the water.

Fig. 9 indicates that similar results were obtained when the base of the applicator was six centimeters above the surface of the water. The intensity at the surface was of course less to start with, and the decrease was more gradual due to the action of the inverse square law. This is evident from the fact that with a point source the intensity changes

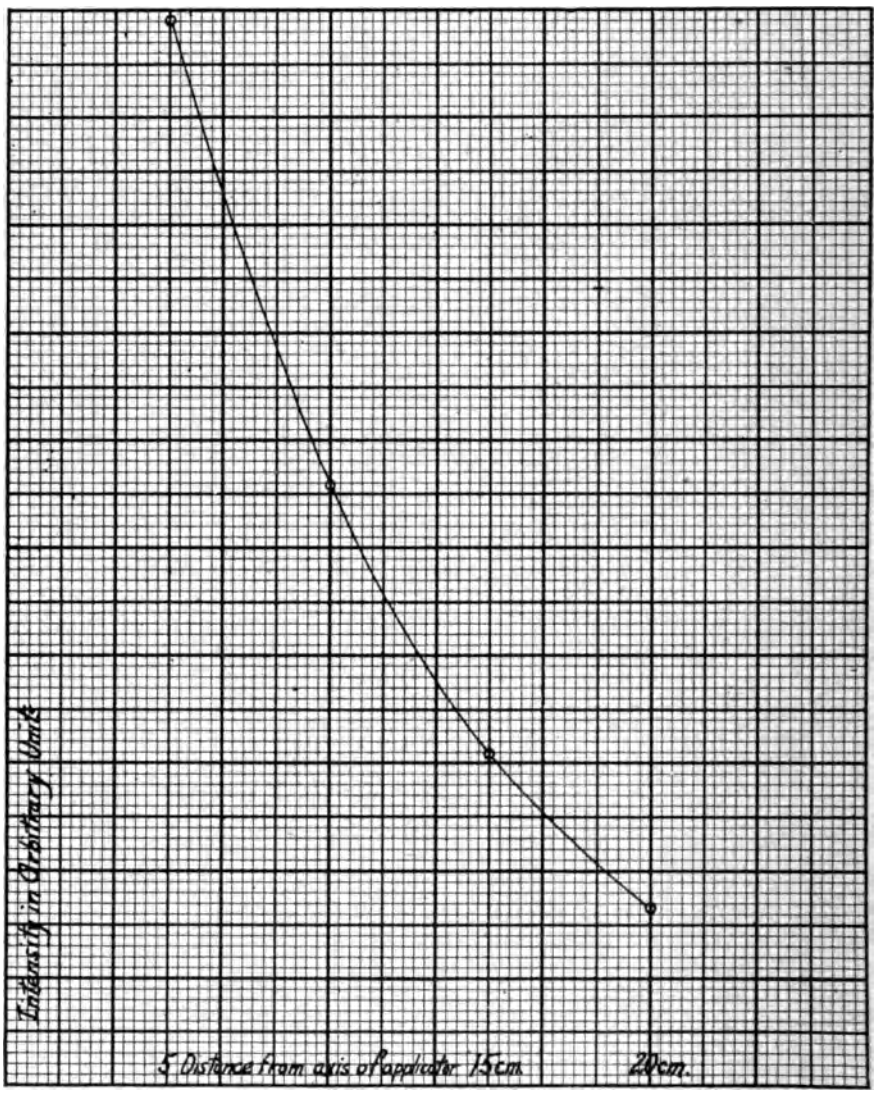

Fig. 10.—Field 5 cm below surface of water. Base of applicator 1 cm. above water.

fourfold in going from five to ten centimeters; one must go, however, a distance of twenty centimeters before the intensity changes again fourfold; i.e., a movement of five centimeters in the first and ten centimeters in the second case is necessary. Furthermore the actual change (not the ratio) is much less in the latter case.

The next series of curves shows the change in the field at a given distance below the surface of the water as we go laterally from a point directly below the center of the radium applicator. The first of these curves (Fig. 10) shows the field at a depth of five centimeters. The decrease here, as one goes out from the axis is rather abrupt, as we

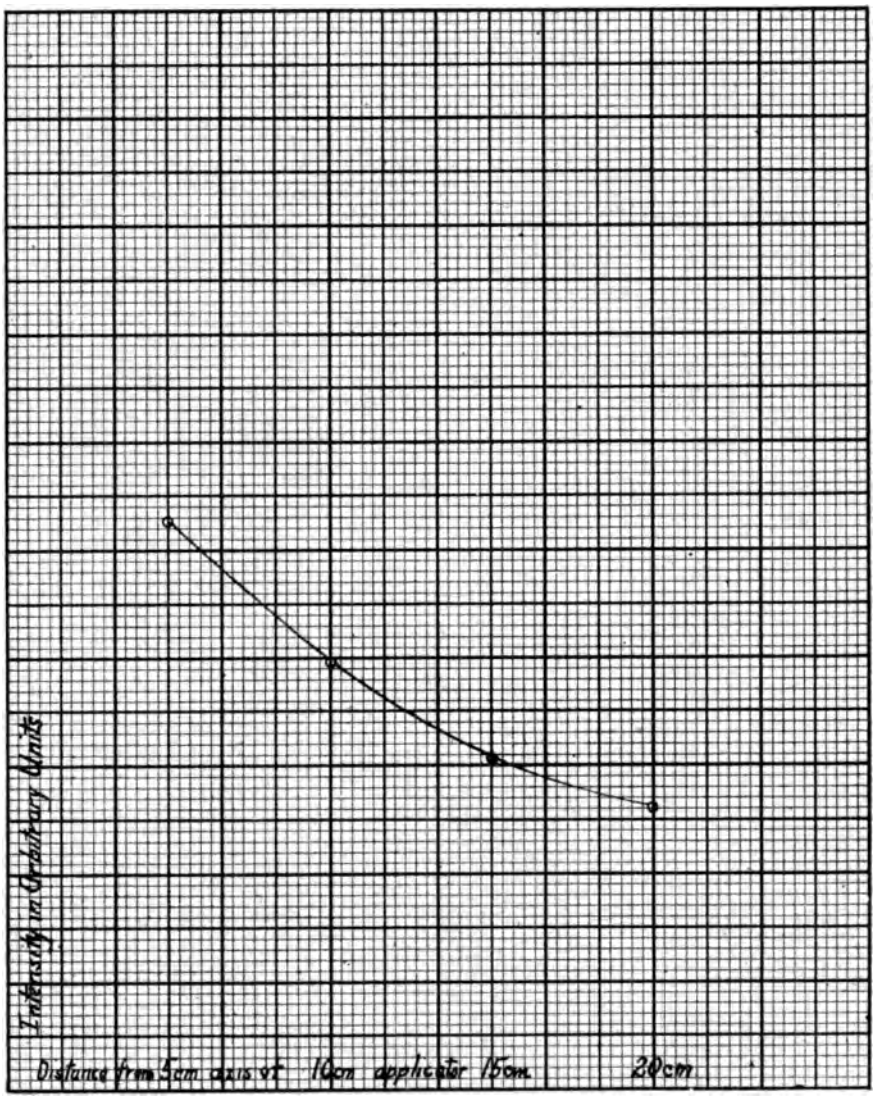

Fig. 11.—Field 10 cm. below surface of water. Base of applicator 1 cm. from water.

should expect, since $13^2 \div 5^2 = 194$, $13^2 \div 10^2 = 269$, i.e., a factor of 1.39 is present from the operation of the inverse square law in the change from five to ten centimeters.

Fig. 11 shows the field at a depth of 10 cm. The decrease is more gradual. $18^2 \div 5^2 = 349$, $18^2 \div 10^2 = 424$. The ratio between these two numbers gives a factor of 1.22. (These factors are not actually the numbers by which the intensities at 5 cm. and 10 cm. distance from the axis should differ, since the radium was not at a point, and there is absorption and scattering).

Fig. 12 shows the field at a depth of 15 cm. The decrease is here more

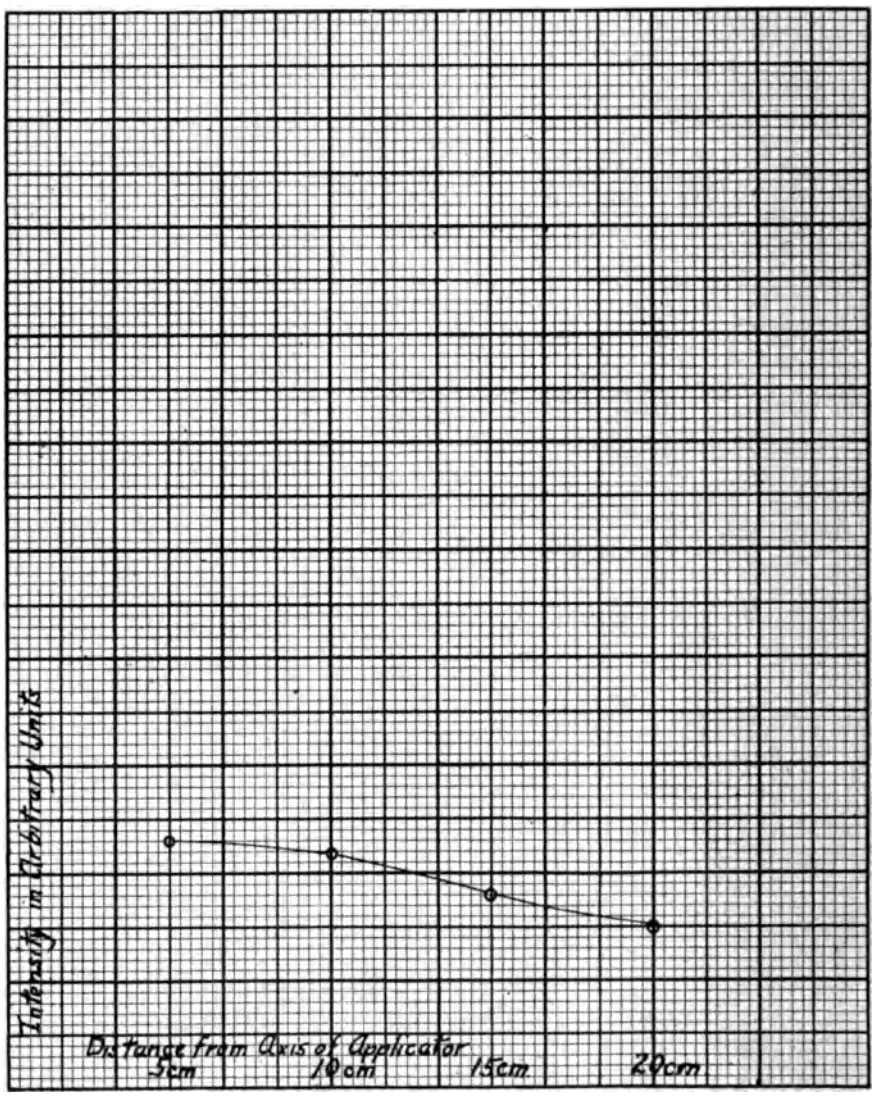

Fig. 12.- Field 15 cm. below surface of water. Base of applicator 1 cm. from water.

gradual still. We find that $23^2 + 5^2 = 554$, $23^2 + 10^2 = 629$. The ratio between these two numbers gives a factor of 1.13. The distance changes relatively (and also actually) less as we go out, perpendicularly to the axis, than when the distance along the axis is small.

Fig. 13 represents the field on the surface. The difference between this curve and the curve in Fig. 12 is extremely marked. The factor here would be 1.84. ($8^2 + 5^2 = 89$, $8^2 + 10^2 = 164$.)

The foregoing series of curves (Figs. 10 to 13) was taken with the base of the radium applicator 1 cm. from the surface of the water; i.e., the radium tubes were a little over 8 cm. from the surface of the water.

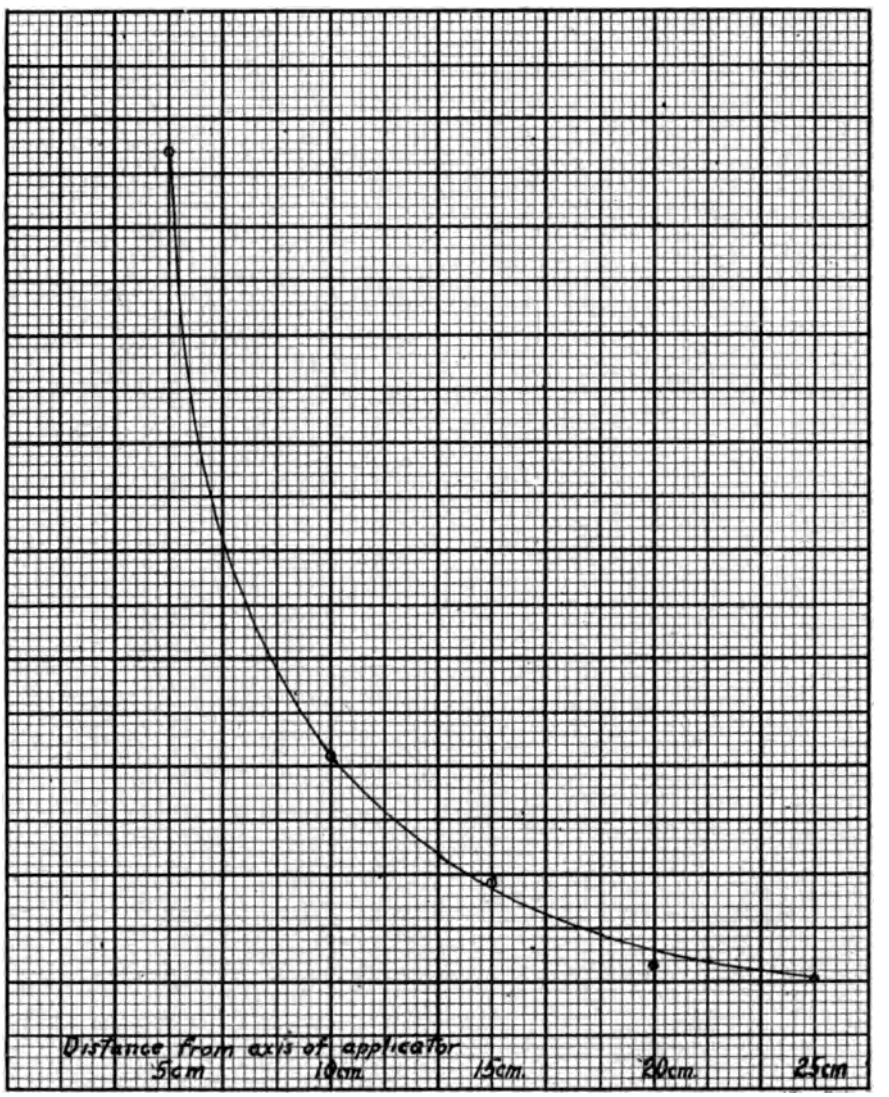

Fig. 13.—Intensity on surface of water. Base of applicator 1 cm. from water.

The curve in Fig. 14 is taken under the same conditions as the previous curve, but is plotted to a different scale horizontally and vertically from the other curves. The distances are taken diagonally from the axis of the applicator.

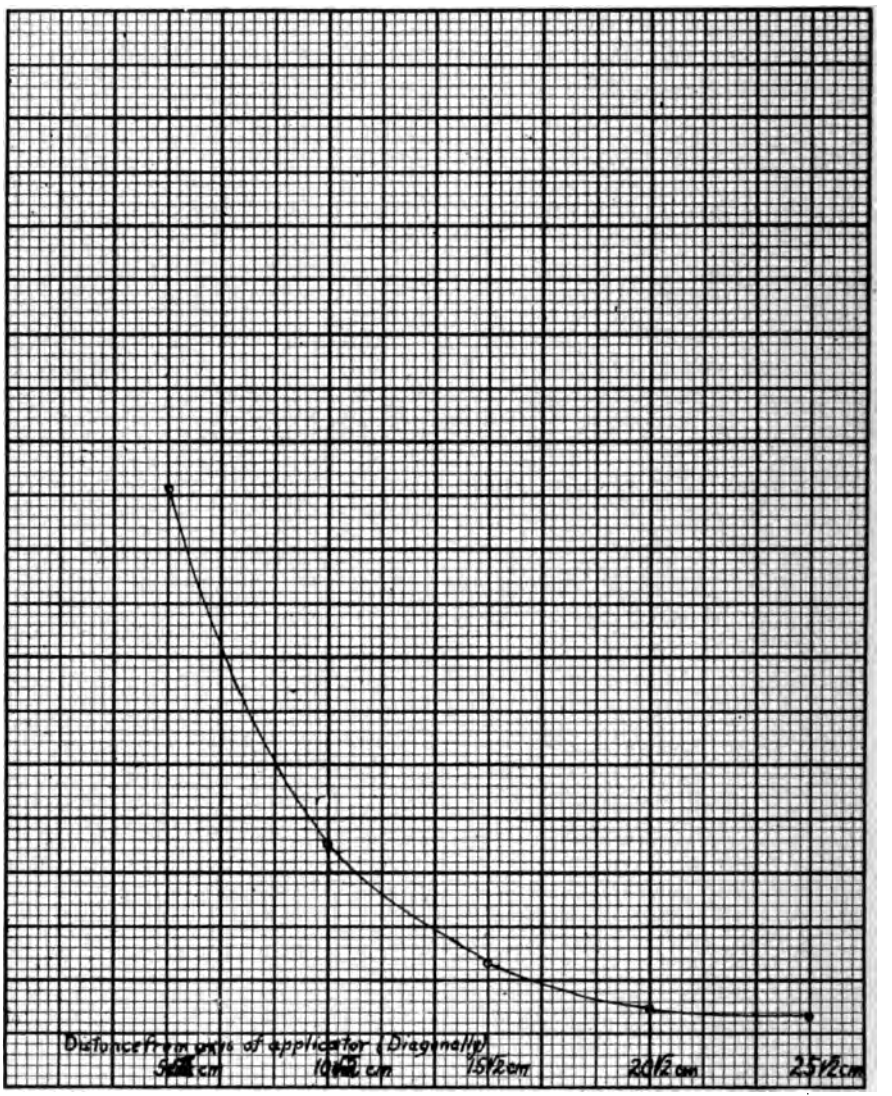

Fig. 14.—Intensity on surface of water. Base of applicator 1 cm. from water.

First Observations of Intensities with the Second Type of Ionization Chambers

We may now discuss the series of curves taken with the second type of ionization chamber. One of these curves was taken as a calibration curve for the chamber. The leak across from the inner electrode to

the ground was not small enough to make conditions favorable; it changed markedly the values obtained from the reciprocals of the times.

A theoretic deduction of the correction to be applied is as follows:

Let c be the current due to the ionization chamber, i.e., that which is to

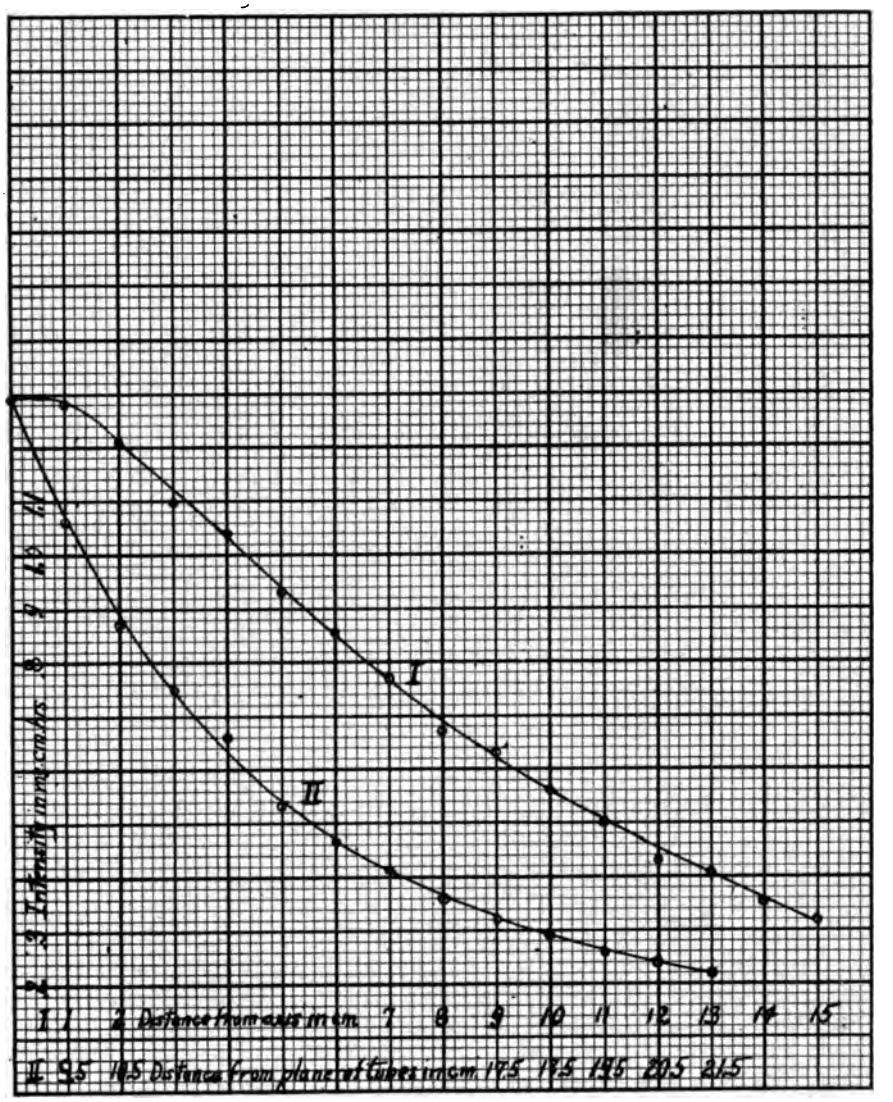

Fig. 15.—Field in air. *I*, parallel to plane of tubes at 3.5 cm. distance. *II*, perpendicular to plane of tubes, along axis.

be measured: $c'V$ that due to the leak from the inner electrode to the ground; V being the voltage to which the leaf has become charged; c'' $(\mathbf{V}'\text{-}\mathbf{V})$ that from high potential to leaf, $\mathbf{V}'$ being the high potential.

Then, neglecting a constant capacity factor,

$$\frac{dV}{dt}=c-c'V+c''(V'-V)$$

$$\frac{dV}{dt}=(c+c''V')-(c'+c'')V$$

$$\int_o^v \frac{dV}{(c+c''V')-(c'+c'')V}=\int_o^t dt$$

$$log\ \frac{(c+c''V')-(c'+c'')V}{c+c''V'}=-(c'+c'')t$$

$$c+c''V'-(c'+c'')V=(c+c''V')e^{-(c'+c'')t}$$

$$c+c''V'=\frac{(c'+c'')V}{1-e^{-(c'+c'')t}}$$

$$c=\frac{(c'+c'')V}{1-e^{-(c'+c'')t}}-c''V'$$

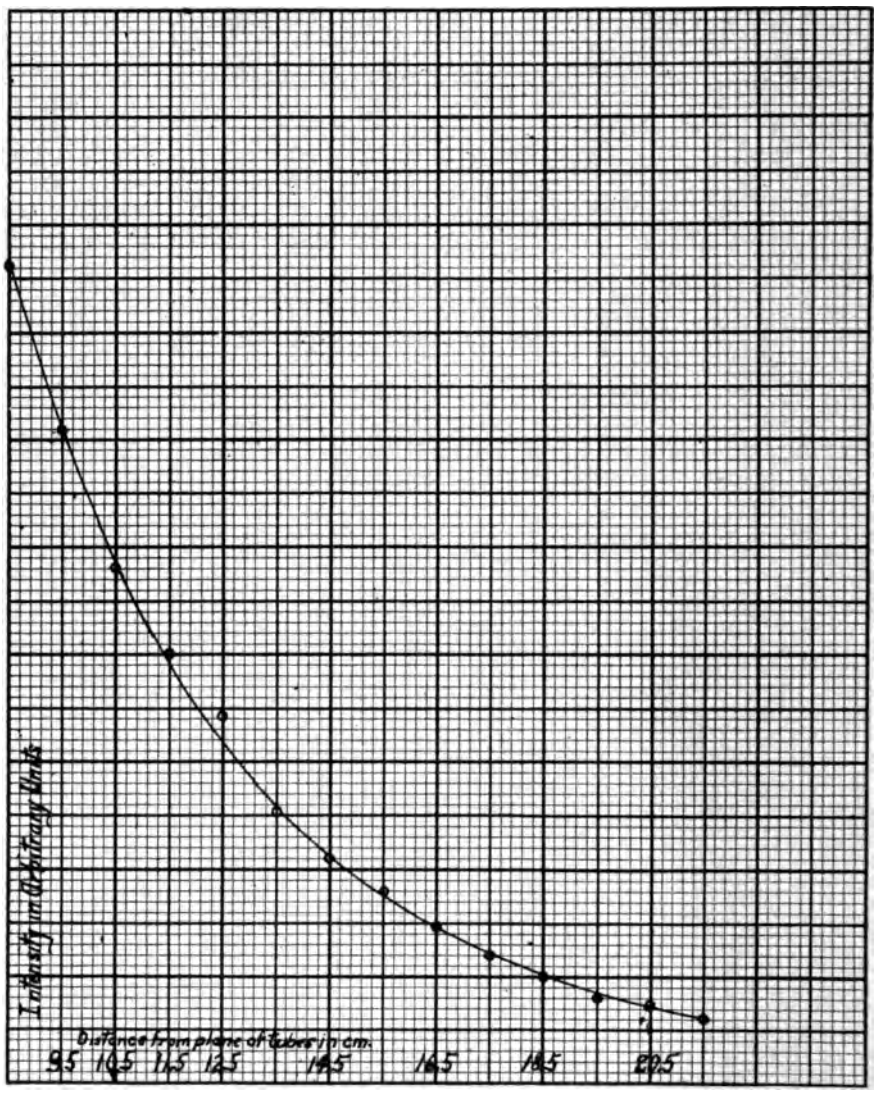

Fig. 16.—Field in air, perpendicular to plane of tubes.

TABLE X

INTENSITIES AT VARIOUS DISTANCES ALONG THE LINE PERPENDICULAR TO THE CENTER OF A 6x6 CM. PLAQUE, WITH 9 TUBES CONTAINING 100 MC. IN ALL

DISTANCES IN CM.	INTENSITIES (THEORETIC VALUES) AT DIFFERENT POINTS ON THE AXIS
8.5	1.29
9.5	1.05
10.5	.866
11.5	.727
12.5	.619
13.5	.533
14.5	.464
15.5	.407
16.5	.360
17.5	.321
18.5	.288
19.5	.259
20.5	.235
21.5	.214

TABLE XI

INTENSITIES AT VARIOUS DISTANCES FROM THE LINE PERPENDICULAR TO THE CENTER OF A 6x6 CM. PLAQUE, WITH 9 TUBES CONTAINING 100 MC. IN ALL
ALL VALUES ARE TAKEN AT A DISTANCE OF 8.5 CM. FROM THE PLANE OF THE TUBES

DISTANCES IN CM.	THEORETIC VALUES	EXPERIMENTAL VALUES (CORRECTED BY CALIBRATION CURVE)
0	1.29	1.28
1	1.28	1.28
2	1.23	1.21
3	1.17	1.10
4	1.09	1.04
5	1.00	.93
6	.91	.85
7	.82	.77
8	.73	.67
9	.65	.63
10	.58	.56
11	.52	.50
12	.47	.46
13	.42	.43
14	.38	.40
15	.34	.35
16	.31	.32

The other curves were then corrected by means of the calibration curve and for air were found to agree very well with the theoretic values.

In Fig. 15, Curves I and II were taken in air. They show the fundamental characteristics of such curves. Curve I is taken at a constant distance from the plane of the tubes and at different distances from the axis. It shows zero slope to start with, gradually increasing gradation, then a point of inflection, and a gradual decrease in slope.

Curve II is taken along the axis; the slope is at first large and gradually decreases.

All curves in air can be regarded as combinations of these two types.

Fig. 16 is the original curve for Fig. 15 II. It was by correcting Fig. 16 to the latter that the calibration was obtained.

Second Series of Observations with the Second Type of Ionization Chamber

The apparatus was now set up a second time. Data were taken which resulted in Fig. 17 for the field in water. The calibration curve obtained

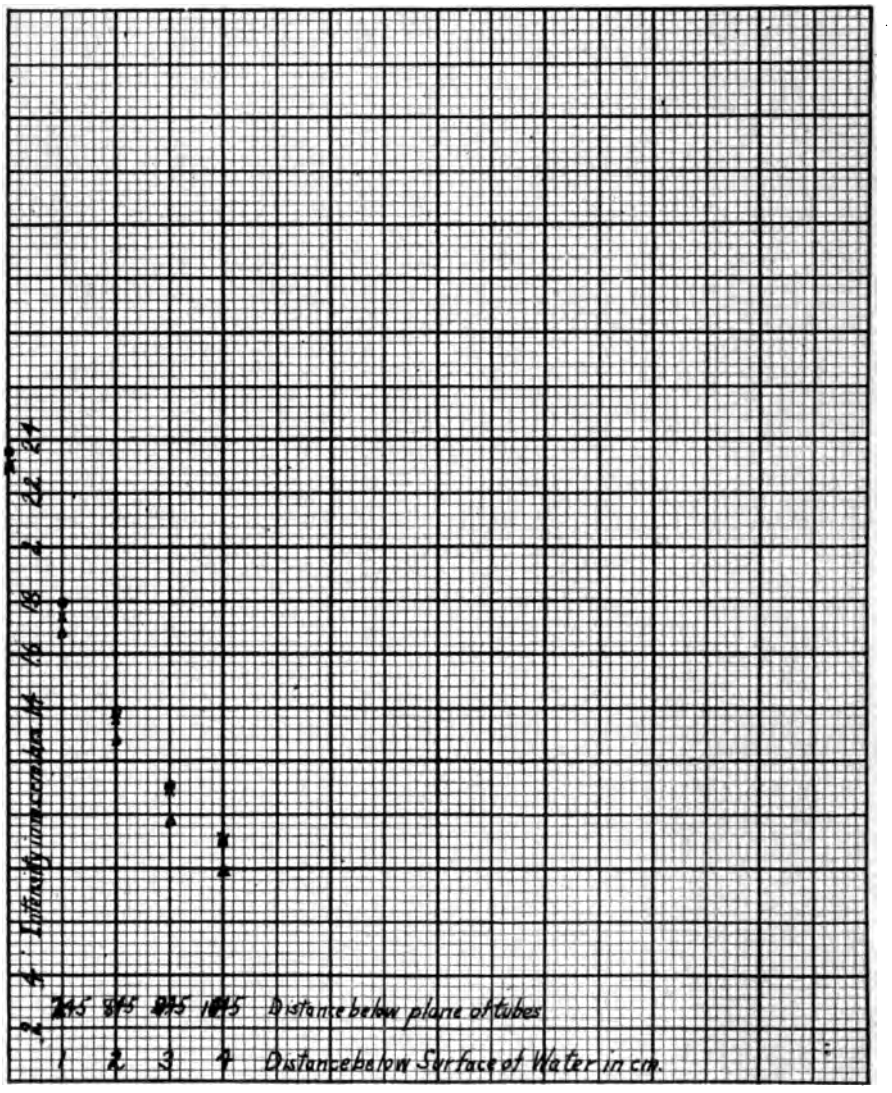

Fig. 17.—Field in water, perpendicular to plane of tubes. o, Experimental values; x, values calculated on the basis of no absorption; △, values calculated on the basis of $\mu = .033$.

in air was almost identical with that obtained previously; it is practically linear, $I = \frac{140}{t} + .253$ fitting the calibration curve with a maximum error of a few per cent.

Data were taken later for depths down to ten centimeters. The applicator used was 10 cm. square and 10.7 cm. high. The base of the applicator was kept at a distance of 3 cm. from the surface of the water, and hence the plane of the tubes in every case was 14 cm. above the surface of the water.

The first column in Table XII gives the distance of the point at which the intensity was measured from the plane of the tubes; the second its distance below the surface of the water. The third column gives the observed value of the intensity. The fourth, the value calculated without allowing for any absorption by the water, i.e., the value which it would have had if there had been no water present. The fifth column is the per cent difference between the value observed and the value calculated on the basis of no absorption. The sixth and eighth columns assume absorption coefficients of .033 and .05 for the water respectively, while the seventh and ninth columns give the percentage differences between the values calculated on these assumptions and the values observed.

TABLE XII

DISTANCE FROM PLANE OF TUBES.	DISTANCE BELOW SURFACE OF WATER.	OBSERVED VALUES.	CALCULATED VALUES. AIR. NO ABSORPTION.	% DIFFERENCE BETWEEN OBSERVED AND CALCULATED.	CALCULATED $\mu = .033$	% DIFF. OBS'D. CAL'CD.	CALCULATED $\mu = .05$.	% DIFF. OBS'D. CAL'CD.
13.50cm.	.05cm.	.570	.506	13	.506	13	.506	13
15.55cm.	2. cm.	.408	.388	5	.363	12	.351	16
16.85cm.	3.3 cm.	.325	.334	−3	.299	9	.285	14
18.35cm.	4.8 cm.	.257	.284	−10	.242	7	.223	15
20.30cm.	6.75cm.	.217	.234	−8	.187	16	.167	30
20.65cm.	7.1 cm.	.210	.226	−7	.178	18	.158	33
21.75cm.	8.2 cm.	.198	.204	−3	.155	28	.135	47
23.15cm.	9.6 cm.	.181	.181	0	.131	38	.112	62
23.95cm.	10.4 cm.	.165	.170	−3	.120	38	.101	69

Hence the same general conclusion was reached in the second series of observations as in the first; viz., that the intensity below the surface of the water was practically the same as though no water were present. This conclusion was now found, however, to remain true down to a depth of ten centimeters. In other words, the increase due to the scattering, under

the conditions used, almost exactly neutralizes the decrease due to the absorption.

As regards the difference between the observed values and those calculated on the basis of $\mu = .033$, the percentage of difference varies from approximately 10 per cent from the skin surface down to a depth of 5 cm. up to 38 per cent at a depth of 10 cm.

Using an absorption coefficient of .05, the variation is from about 15 per cent to about 70 per cent.

Final Series of Observations with the Second Type of Ionization Chamber

Other readings taken with various types of radium applicators and different amounts of radium arranged in various ways appeared to give the same result with the type of chamber used; viz., there was seemingly little change in the gamma ray intensity due to the presence of water. There was possibly a change of about ten per cent in a few readings down to a depth of ten centimeters. Below 10 cm. a slight decrease below the value that would have been obtained in air was noted.

Fig. 18 shows the relatively insignificant effect of the presence of a layer of water 3 cm. thick as compared with a change of 3 cm. in the distance of the radium from the point at which the intensity was measured. All the curves give the variations in the field as one passes (parallel to the plane of the tubes) laterally from the axis of the applicator.

Curve I (Fig. 18) is taken with the base of the applicator 2 cm. above the water and 5 cm. from the ionization chamber, i.e., with the ionization chamber 3 cm. deep in the water. The water was then lowered 3 cm. keeping the radium in the same place (i.e., base of applicator 5 cm. from water and ionization chamber, latter being on surface of water). Curve II (Fig. 18) was then taken. The total effect due to three cm. of water (with no change in distance of radium) between the radium and the object radiated would thus appear to be small.

The applicator was then lowered 3 cm. (i.e., base 2 cm. above water and ionization chamber). Curve III Fig. 18 was then taken. This curve shows the relatively large effect due to this change in distance.

Curves I and II thus refer to the same distance of chamber from radium, and differ only in the amount of water between the two. Curves I and III, on the contrary, refer to the same distance of surface of water from radium, and differ only in the depth at which the chamber was placed.

That the difference in the rate of variation of the field depends markedly on the distance of the radium is shown very well by Curves II and III. The rate of change, is, for a point source, as one leaves the axis, inversely proportional to the square of the distance from the radium along the axis, while the relative change varies inversely as the distance.

On trying to apply the null method mentioned by Makower and Geiger (previously referred to) it was found that with the condenser at hand the

leak over the surface of the insulation (which was of ebonite) was very great compared to the current to be measured. As a result we gave up for the time being at least, what seemed to be a promising method of getting rid of every leak except that in the electroscope. With a proper condenser the method should be as good as any yet worked out.

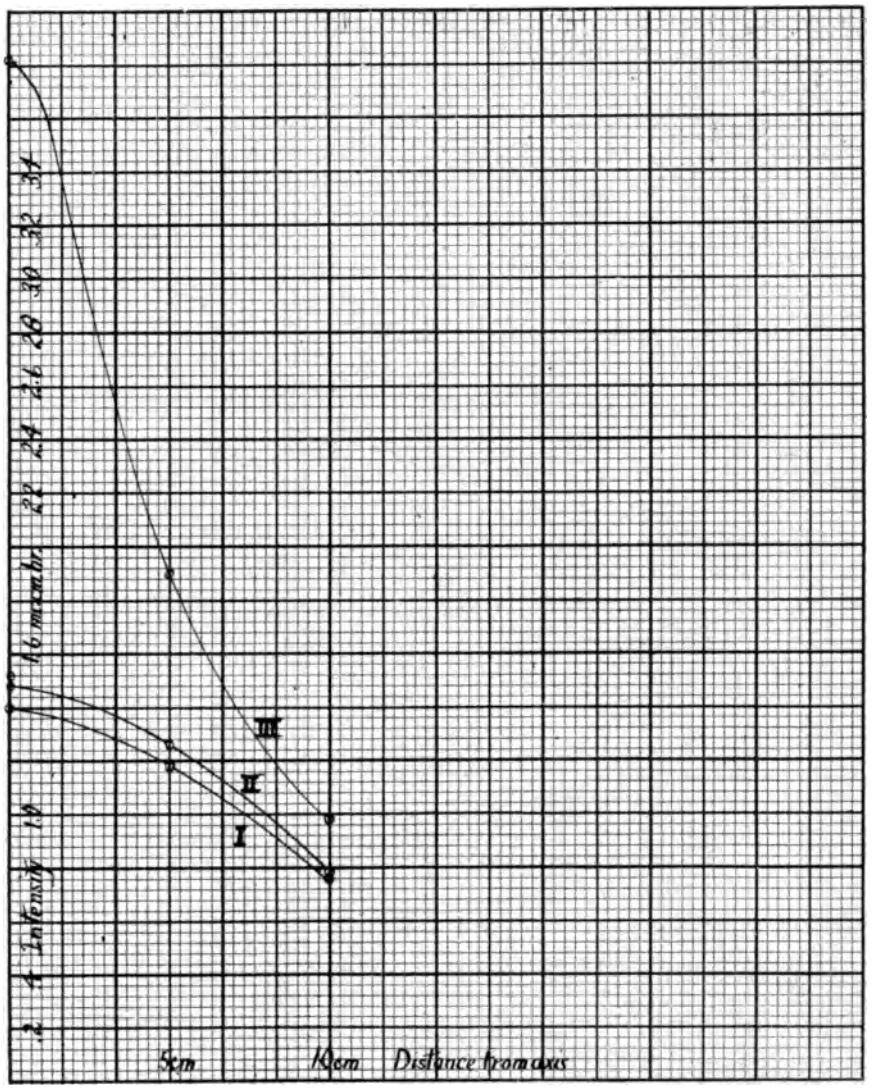

Fig. 18.—Diagram showing change in intensity due to distance as compared with change in intensity due to absorption in water.

Other possible improvements in the technic of the experiments may be mentioned. The electroscope could be evacuated, or shielded with a lead screen. The capacity of the whole system could be decreased by using larger connecting tubes or finer wires; by joining successive wires di-

rectly and pouring sulphur over the connections the insulation would be improved. The use of thinner tubing would decrease the weight of aluminum in the guard tube.

One possibility of error must now be mentioned. In case the ionization chamber allows secondary beta rays from the water to enter in sufficient quantity to modify the readings, the results of the foregoing tests may be misleading, since the effect would be to increase the values in water relative to those in air. This does not, however, seem to be probable.

The whole series of experiments could be repeated with an ionization chamber made extremely thin in order to intercept and measure the beta rays instead of the gamma rays.

The chamber suggested would not be thick enough to scatter the gamma rays appreciably as may happen with the type of chamber that we have been using.

Although under these circumstances both beta and gamma rays would take effect, the error due to the gamma rays would probably be so small as to be practically negligible.

CHAPTER VIII

PHYSICAL AND CHEMICAL EFFECTS OF RADIUM RAYS

In this chapter will be considered briefly some of the physical and chemical effects that the radiations from radium may cause. Most of these effects are due to the action of the alpha and beta rays although they may also result from the gamma rays.

1. IONIZATION OF GASES

The rays have the power of discharging electrified bodies such as the electroscope, the rate of discharge depending on the intensity of the radiations. In order to explain this phenomenon the theory has been advanced that the rays produce in the air negatively charged carriers called "ions" which render the air a good conductor of electricity. This property of producing "ions" is known as that of ionization. The alpha rays have a marked ionizing effect; the beta rays have only one or two per cent of the ionizing effect of alpha rays, while the ionizing effect of the gamma rays is only a few per cent of that of the beta rays. Locally alpha rays have intense ionizing power. Beta and gamma rays have a less intense local action but this is distributed over a larger space. The total ionizing effect of each of the three kinds of rays is probably about the same. The ionizing effect of the gamma rays is probably due to the secondary beta rays which are produced by the absorption or "stopping" of the gamma rays. In the chapter on measurement of the beta-gamma ray activity of the radiations this subject has been considered in more detail.

2. PENETRATION OF OPAQUE MATTER

The degree of penetration possessed by the radiations may be shown by the electroscope. A radium salt exposed freely in an electroscope causes a very intense ionization of the air and the charged gold leaf moves quickly across the field of the microscope. If the radium preparation is covered with a piece of aluminum foil or merely with a sheet of note paper, the ionization is much less intense and the gold leaf moves much less rapidly. With ten sheets of note paper covering the salt the ionization is about one half as intense as with one sheet. It is evident that the interposition of the note paper cuts off the most readily absorbable rays which have a marked ionizing effect. By covering the radium salt with various thicknesses of metal, rays of widely different penetrating power may be distinguished. The rays most easily absorbed

are known as the alpha rays, those less easily absorbed are the beta rays, while those least easily absorbed are known as the gamma rays.

Alpha rays are absorbed by about .089 mm. of epithelial tissue. They are therefore of little or no therapeutic importance. The most penetrating beta rays are half absorbed by 0.1 mm. of lead and to the extent of 99.9 per cent by 1 mm. of lead. According to Rutherford they are completely absorbed by 2 mm. of lead. The hardest beta rays, after penetrating 1 cm. of epithelial tissue, lose about 94 per cent of their energy. In other words, on account of absorption their quantity after passing through 1 cm. of tissue, is only about 6 per cent of that at the surface. The gamma rays are absorbed to the extent of 40 per cent by one cm. of lead and to the extent of 99.4 per cent by 10 cm. of the same material. The gamma rays from thirty milligrams of radium can still be detected by the electroscope after passing through 25 cm. of lead or 30 cm. of iron. According to the investigations of Giraud, gamma rays are reduced to one-half their intensity after passing through 20.4 cm. of water, 18.3 cm. of blood serum, 14.4 cm. of blood or 7.6 cm. of muscular tissue.

Using lead as a test of absorbing power, hard gamma rays are about thirty times as penetrating as hard x-rays from the Coolidge tube. Using water (tissues) as a standard of comparison hard gamma rays are slightly more than four times as penetrating as hard x-rays.

Advantage may be taken of the fact that the alpha, beta and gamma rays are stopped or absorbed by varying thicknesses of metallic and non-metallic substances. By placing between the radium and the tissues different thicknesses of such materials, varying portions of the beta and gamma rays may be filtered out. The biologic effects of the rays will evidently vary according to the type and quantity of rays that penetrate the screen and are absorbed by the tissues.

3. PRODUCTION OF HEAT

Radium liberates heat spontaneously and continuously. Compounds of radium maintain themselves at a temperature several degrees higher than the surrounding atmosphere. In one hour one gram of radium element spontaneously generates sufficient heat to elevate the temperature of 136 grams of water one degree centigrade.

"The emission of heat from radium and other radioactive substances is in a sense a secondary effect for it is a measure of the energy of the radiations expelled from the active matter which are absorbed by the active matter itself and the envelope containing it." (Rutherford.)

The alpha particles produce the greatest heating effect, furnishing 125 calories of the 136 calories produced by one gram of radium in one hour. The beta rays bear 4.5 and the gamma rays 6.5 of the remaining 11 calories.

4. EMISSION OF LIGHT

All radium compounds are feebly self-luminous in the dark. This phenomenon is probably due to the presence in preparations containing radium of impurities which phosphoresce under the constant bombardment of the rays. This luminosity varies under different conditions. Radium preparations lose a large amount of their luminosity upon exposure to damp air, but regain it again when the salts are dried.

5. PHOSPHORESCENCE AND FLUORESCENCE

Various bodies phosphoresce or fluoresce under the influence of radium rays. The large majority of substances that exhibit this property belong to the alkali metals or alkali earths.

Among the many different substances that become luminous when exposed to the rays are willemite (zinc silicate), kunzite and sparteite, barium platinocyanide, hexagonal zinc blende, certain kinds of diamonds, etc. The property possessed by radium rays of inducing phosphorescence has been taken advantage of by Crookes in devising the spinthariscope. In this little instrument a minute quantity of radium is enclosed in a tube which has a zinc sulphide screen at one end and a magnifying lens at the other. Upon looking through the lens in the dark the screen appears as a dark field lighted up by rapid scintillations. The latter are due to the continuous shooting out of alpha particles which cause, by impact, the zinc sulphide to fluoresce.

Certain bodies, e.g., fluor-spar, when exposed to radium rays become luminous only when heated—this phenomenon being known as "thermoluminescence."

The alpha rays are the most active in causing fluorescence, the beta and gamma rays being much less powerful in this respect.

6. PHOTOGRAPHIC ACTION

All three types of rays have a marked action on the photographic plate, the beta rays being less energetic than alpha rays and the gamma rays less active than either of the others. Radiographs made with gamma rays, however, are better defined than those made with beta rays mixed with gamma. Radiographs made with x-rays are much more clear and distinct than those made with radium radiations.

7. COLORATION OF VARIOUS SUBSTANCES

Ordinary soda glass is colored violet or even black after long continued exposure to the rays. Other kinds of glass may become brown or yellow. The capillary glass tubes in which the emanation is confined for thera-

peutic use as well as certain parts of the glass tubing of the emanation apparatus itself thus turn violet after prolonged use. Plates of mica may be colored brown or black. Joly showed that the "pleochroic halos" of mica were due to radioactive effects. Diamonds may temporarily be colored rose, yellow, blue or green. It was at one time thought that the change in color produced by the rays in barium platinocyanide might serve as an index to the therapeutic effects of the rays just as x-rays may be measured by the Saboraud-Noiré pastiles. No practical results have been obtained, however, from this method of measurement.

Coloration effects are due especially to the alpha particles but the beta and gamma rays may also act in producing them.

The change in color due to alpha rays is limited to a surface layer, as, e.g., in the case of glass when it is exposed, while the beta and gamma rays color the deeper layers of the substance as well.

8. OTHER CHEMICAL EFFECTS

In addition to the coloration of certain bodies just referred to, radium rays, especially the alpha particles, may produce various chemical changes in numerous substances. Only a few of these effects will be mentioned here.

Ozone may be produced from oxygen. Various metals, such as lead, mercury, etc., when exposed in air, are rapidly oxidized.

Water is decomposed by the radiations into hydrogen and oxygen. Organic matter, in general, is decomposed gases being given off. In the apparatus for the extraction and purification of radium emanation for therapeutic use stopcock grease is not used, owing to the decomposition of the grease by the radiations with the production of carbon dioxide.

Paper, rubber and other fabrics exposed constantly to the radiations, crack and become reduced after a time to powder. The flexible type of radium applicator made of linen or rubber becomes more or less disintegrated after some months and must be remade. Many other chemical reactions due to the radiations have been observed but for details of these and many other interesting phenomena the reader is referred to special works on radioactivity.

CHAPTER IX

BIOLOGIC EFFECTS OF RADIUM RAYS

EFFECTS OF RADIUM RAYS ON LIVING CELLS

Numerous experiments have demonstrated the effects of radium rays on living cells of both the vegetable and animal kingdoms. In this and the succeeding chapter we shall give the results of some purely experimental investigations which have a direct bearing, however, on the use of radium in disease.

1. Effects on Bacteria

Aschkinass and Caspari, Chambers and Russ, Green, Pfeiffer and Friedberger, Hoffman, Strebel, Strassmann, and many other investigators have carried out experiments to determine the effect of the rays or of the emanation on bacteria.

Pfeiffer and Friedberger exposed gelatin cultures of cholera and typhoid bacilli and of anthrax spores to 25 mg. of radium bromide at a distance of 1 cm. The beta and gamma rays were used. The growths within a certain superficial area were destroyed in 16, 48, and 72 hours, respectively. Strassmann studied the effect of the rays from 10 mg. of radium bromide upon various organisms. The time required to kill B. prodigiosus, streptococcus, staphylococcus, and B. tuberculosis was found to be 24, 24, 48, and 108 hours, respectively. Chambers and Russ prepared emulsions of various organisms in distilled water. Emulsions of B. coli communis, staphylococcus pyogenus aureus, B. pyocyaneus, B. anthrax and B. tuberculosis were exposed either to a known intensity of beta rays or to a measured concentration of radium emanation. The beta rays from as small a quantity as 7 mg. radium bromide were found to have a bactericidal effect. In estimating the effect of the emanation a known volume of the emulsion of the organism was removed from the influence of the emanation at different periods and planted upon agar-agar. With a concentration of the emanation amounting to 5 mc. per c.c., the number of organisms being approximately one million per c.c., a sterilizing effect was noted on the above organisms in periods of from sixty-five minutes to four hours. A possible error in these conclusions lies in the fact that the emanation produces ozone which may be the bactericidal factor. From these and the general trend of many other experiments it has been concluded that the rays from radium have distinct bactericidal properties when allowed to act in sufficient doses outside of the body of the host. As to the effect on bacteria in tissues, however, no results have been obtained experimentally that would indicate that bacteria may be actually

destroyed by radium rays without serious injury to the tissues themselves. It may be mentioned, however, that Flemming and Krusius observed inhibition of the growth of bovine tubercle bacilli placed on the cornea or in the anterior chamber of the eye.

In military surgery beneficial effects in checking suppuration in deep wounds have been noted. Improvement has been noted by the writer and others following the introduction of radium tubes into tuberculous sinuses, etc. Certain chronic ulcers discharge less freely after radiation. These favorable effects are probably to be attributed, however, to the effect on the tissues rather than to the actual bactericidal effect of the rays. With our present knowledge of the effect of the rays on the higher types of living cells no practical results in the actual destruction of bacteria in tissues without destroying the tissues containing them can be expected. Long before the bacteria, which are highly resistant vegetable organisms, can be destroyed, the more sensitive tissues of the animal organism will be irreparably damaged.

2. Effects on Seeds and Plants

Abbe, Matout, Molisch, Fabre and many others have recorded interesting experiments on seeds and plants. Abbe exposed wheat grains to mixed beta and gamma rays for different lengths of time and at varied distances. "The universal effect was a depression of growth exactly in proportion to both time and distance." Matout exposed the seeds of cress and white mustard to the beta-gamma rays for a week and found that they had lost their power of germination. Molisch exposed the buds of syringa vulgaris to the beta rays and found that their growth was favored when in the resting stage but hindered when in the growing state. Fabre found that a flowering lily, irradiated with strong doses, had its development stopped completely.

Further illustrations of the effect of the rays on various forms of vegetable life may be found in special articles referred to in the bibliography.

3. Effects on the Lower Forms of Animal Life

Observations of the effects of the radiations on certain lower forms of animal life (protozoa, etc.) have been made by Bohn, Halberstaedter, Willcock, Zuelzer and many others. Only a few of these experiments can be referred to here.

Halberstaedter and his coworkers radiated trypanosomes and observed particularly the effect both on their subsequent motility and their power of infecting animals. With the doses used, the motility of the trypanosomes was apparently unaffected. The rays checked, however, their power of reproduction so that infection did not, as a rule, occur. From this it was inferred that the rays acted particularly on the nuclei which are the elements responsible for the propagation of the trypanosomes.

Halberstaedter, therefore, inferred that the radiations affected and destroyed the reproductive functions of the organisms before the nutritive functions were injured.

The effects on the developing forms of some of the lower animals have been observed by Bohn, O., G. and P. Hertwig, Thur, and many others. Bohn investigated the effects on the spermatozoa, ova and larvæ of the sea urchin. Spermatozoa were rendered less active and finally killed. Ova and larvæ developed more slowly and irregularities of development and form were observed.

Paula Hertwig investigated the effect of radiations on the development of the ova of ascaris megalocephala, particularly with respect to the nuclear changes. Development was slower than normal and irregularities of form were noted. The chromatin of the nuclei was especially affected and even destroyed.

Thur observed the effect of radium rays upon chick embryos and later upon the embryos of the gold fish. Retardation and irregularities of development and the production of monstrosities were noted. O. and G. Hertwig have made an extensive series of observations upon the spermatozoa, ova and larvæ of frogs. Sufficiently long exposures disorganized the chromatin of the spermatozoa. Ova that had been fertilized with normal spermatozoa and then irradiated developed much more slowly than normally and exhibited many irregularities of development. Ova that were fertilized with irradiated spermatozoa also showed many abnormalities of development. It is of interest to note that O. Hertwig found that certain chemical agents produced irregularities of development and abnormalities of form that were nearly identical with those due to radiation.

Radium cannot therefore be regarded as producing changes in these developing forms that are absolutely characteristic.

For a fuller account of these and many other interesting observations of the effects of the rays on various organisms the reader is referred to the articles mentioned in the bibliography.

4. Effects on the Various Tissues of the Higher Animals

Broadly speaking, all three types of radium rays, if allowed to act in sufficient doses, produce inflammation and even destruction of the irradiated tissues. In a subsequent chapter devoted to the subject of "reaction" we shall refer to two different kinds of response on the part of the tissues that are to be observed after the application of radium to the skin. We shall then emphasize the fact that very important modifications of vital tissues may be brought about either by a selective or by an inflammatory effect of the rays. We mention this at this point in order to correct an erroneous belief that radium rays in order to cause pathologic tissues to disappear necessarily cause inflammation. Most of the histologic examinations of irradiated tissues have been made in

cases in which a more or less intensive inflammatory effect had been produced. The "selective" effect of the radiations, resulting in modifications of tissue that are not associated with visible inflammation is just as important, however, from a clinical point of view, as the inflammatory effect.

EFFECTS OF THE RAYS ON THE SKIN

The macroscopic or clinical appearance of the inflammation of the skin due to radium rays will be discussed in the main in a later chapter under the subject of "reaction." Here we may consider the histologic changes occurring in the skin after experimental radiations.

These changes have been observed and described by Halkin, Thies, Guyot, Dominici and Barcat, and many others. The animals used in the various experiments were pigs, guinea pigs and mice. Thies exposed an area of human skin.

We may first briefly epitomize the histologic findings of Dominici and Barcat who have accurately stated the conditions of their experiments. These two authors made their investigations with six mg. of radium bromide contained in a "varnish plaque" and spread over a circular surface two cm. in diameter. In one series of experiments no screen was used, the radiations consisting, therefore, of mixed beta and gamma rays (beta rays probably 90 per cent, gamma rays 10 per cent). Ten exposures of five minutes each were given on successive days, guinea pigs being used. The clinical effects appeared ten days later. These consisted of erythema followed by ulceration and crusting. The crust fell off between the fifth and sixth week. The healed irradiated area then appeared as a depigmented, hairless, smooth and supple scar.

Histologic Findings Eight or Ten Days after the Commencement of Exposures

In the epidermis, evidences of inflammation were noted. The nuclei of the epithelial cells showed enlargement or irregularity of outline together with thickening of the chromatin fibrils and the nucleolus. Intercellular edema was present.

Histologic Findings Ten or Fifteen Days after the Commencement of Exposures

Epidermal desquamation was noted and there were evidences of a granular and pigmentary degeneration in the sweat and sebaceous glands and in the hair follicles. During this same period the corium was the seat of an intense congestion and of a beginning embryonic transformation.

Histologic Findings Thirty or Forty Days after the Commencement of Exposures

Two phases were noted. (1) "The phase of embryonic regression" and later (2) "the phase of fibrosis." During the first phase the epidermis was restored but the hair follicles and glandular structures were permanently destroyed. The corium had undergone such changes that its normal structure was apparently lost. There was a temporary reversion to an embryonic type. The connective tissue and the elastic tissue underwent a transformation, giving place to innumerable branching connective tissue cells. These had ramifying and anastomosing processes. The smooth muscle fibers underwent similar changes, being indistinguishable from the other embryonic tissue cells. The small blood vessels showed a tendency to revert to embryonic forms. The endothelium acquired the plasmodial character of the embryonic type. The walls of the vessels themselves appeared to be made up of fusiform and stellate cells continuous both with the extrinsic proliferating connective tissue cells and with the endothelium itself. In short, the connective tissue and vascular system of the corium became converted into an embryonic and angiomatous type of tissue.

In the second phase, fibrous connective tissue redeveloped. There was a tendency toward the formation of a fibrous scar which differed, however, both from the normal corium and from the usual postinflammatory sclerotic tissue. From the former it was distinguished by the regularity of the superimposed connective tissue fibers and the intervening cells and by the fact that the fibrous tissue formed lines parallel with each other and with the surface. From the latter it was distinguished by the remarkable regularity of the sclerotic tissue and by "the absence of fibroid perivascular rings and of vascular obliteration." Six or seven months after the commencement of the exposures, connective tissue fibers largely replaced the cellular elements but there was the same remarkable regularity and parallel arrangement of the sclerotic tissue.

In a second series of experiments carried out by Dominici and Barcat the same radium plaque screened with 0.5 mm. of silver was used. As this screen filtered out more than 96 per cent of the hard beta rays, the gamma rays were responsible for the main changes. After an exposure of fifty minutes no changes were observed. After an exposure of fourteen hours, there were found histologically an enlargement of the nuclei of the cells of the epidermis and evidences of congestion of the corium. The latter condition was accompanied by a slight hypertrophy of the nucleus and cytoplasm of the connective tissue cells. After an exposure of two or three days there was superficial but temporary destruction of the epidermis. The corium displayed histologic changes that were not to be distinguished from those occurring after an exposure of fifty minutes to the unscreened apparatus.

Lazarus-Barlow has carried out a series of experiments to determine the histologic effects of radium rays on columnar and squamous epithelium. Two tubes, one containing 92 milligrams and the other 38 milligrams of radium bromide (about 49 milligrams and 17 milligrams of radium element) were chosen and allowed to act under the conditions described below for thirteen and one-half and thirty minutes, respectively. The two tubes, having nearly the same screening of platinum and acting under the above conditions(i.e., a larger quantity for a shorter time and a smaller quantity for a longer time) produced the same total amount of ionization. From this standpoint, therefore, the dose was considered as being the same from each tube. Each tube was inserted into the rectum of a series of rats so that 3 different areas covered by 3 different kinds of epithelium were affected, viz., the rectum (columnar epithelium), the anus (moist squamous epithelium) and the under surface of the tail (dry squamous epithelium). The animals were killed so that the effects on the first, second, third, seventh, eighth and ninth days after exposure could be studied. The chief effects were the following:

Columnar epithelium region: 92 mg. acting for 13½ minutes produced in general less inflammatory changes than 38 mg. acting for thirty minutes. This was found to be the case during every period—first to ninth day of the examination.

Immediately adjacent to the tube, more disturbance of mitosis but less inflammatory reaction was observed from the effects of the 92 milligram tube. At a short distance from the tube, less disturbance of mitosis and less inflammatory action was produced by the 92 milligram tube. Degenerative effects, however, such as desquamation, mucous formation, mucoid degeneration, and nuclear changes were more marked as a result of the action of the 92 milligram tube.

In the moist squamous epithelium region the reverse of the above findings was noted. Thirty-eight milligrams acting for thirty minutes produced more changes in the cells—reduction in number of mitoses, swelling of the nuclei and loss of staining qualities—than 92 milligrams acting for thirteen and one half minutes. There were no inflammatory changes.

In the dry squamous epithelium region also the 38 milligram tube in thirty minutes produced more marked alterations in the cells, such as inhibition of mitosis and loss of staining qualities, than the 92 milligram tube in thirteen and one-half minutes. The sphincter ani muscle underlying the epithelium was also more affected by the 38 milligram tube acting for thirty minutes.

In another series of experiments, the effect of rays of different character, obtained by varying the thickness of the screens covering the tubes, was studied. The 92 milligram tube was used but was covered with platinum screens varying in thickness from 0.5 mm. to 2 mm. When a thickness of 0.5 mm. of platinum is used the hard beta rays accompany the total gamma radiation. When a thickness of 2 mm. of platinum is

used the hard beta and soft gamma rays are eliminated, only the hard gamma rays acting. The radium was maintained at the same distance from the tissues in the different experiments by coating the screens with paraffine wax so that their outside diameter was uniformly 8 mm. The time factor of the exposures was varied so that each dose produced the same total ionization. The difference in the exposures therefore consisted only in the different quality of the rays employed. Under these conditions, the epithelium and subepithelial tissues showed greater damage as a result of exposures made with the thinner screens (hard beta plus gamma rays) than with the thicker screens (hard gamma rays).

In still another experiment, the same two tubes containing 92 and 38 mg., respectively, were used. The 92 milligram tube was allowed to act for one hundred and eight minutes and the 38 milligram for two hundred and forty minutes. Measured by the total amount of ionization produced, the dose with each tube was the same. Each tube was inserted into the lower end of the rectum of a rat so that both this part of the rectum and the adjacent parts of the tail were exposed to the rays. The two animals were killed on the ninth day after the exposure. The chief effects were the following:

In the columnar epithelial cell region the 38 milligram tube acting for two hundred forty minutes produced more destructive effects than did the 92 milligram tube acting for one hundred eight minutes. The mucous membrane in contact with the tube in some places sloughed away.

In the squamous epithelial cell region the effects were reversed. Here the 92 milligram tube produced more marked inflammatory changes and destruction of squamous cells in one hundred eight minutes than did the 38 milligram tube acting for two hundred forty minutes.

The following inferences may be drawn from these experiments: Inasmuch as less damage was ordinarily done to the normal columnar epithelium regions when the quantity factor was large and the time factor small, this general method of procedure may be adopted in making therapeutic applications to these regions.

In the case of squamous epithelial cell regions, the reverse effects were noted, i.e., less damage was done to normal tissues by the smaller quantity acting for a longer time. In the treatment of these regions therefore it is probable that a smaller quantity allowed to act for a longer time may be theoretically used with advantage. It must be emphasized, however, that conclusions drawn from these and similar experiments must not be accepted too literally.

Practical experience has shown conclusively that not less than 50 milligrams of radium element and in some instances more than twenty times this quantity should be used in dealing with malignant conditions. One must not be misled, therefore, into assuming that very small quantities of radium are capable of seriously affecting large masses of malignant tissue no matter how prolonged may be the exposure. According to

some authors, too small a quantity of radium may even do serious harm by stimulating cellular activity.

EFFECTS ON THE SPLEEN, LYMPHATIC GLANDS AND BONE MARROW

The action of radium rays on the normal spleen, the lymphatic system and the bone marrow has been investigated by Thies, Heinecke and many others. Thies irradiated white mice "in toto" with 20 milligrams of radium bromide for various periods. After a prolonged exposure (nine to eleven days) he found that the spleen, the lymphatic glands, and solitary lymph follicles showed an absence of lymphocytes. The spleen was diminished in size and small masses of pigment were found throughout the pulp and especially around the arteries. The supporting connective tissue was increased. Heinecke found similar changes in the spleen as the result of irradiations. This author irradiated the exposed spleen of rabbits and guinea pigs for as short a period as five seconds and detected pronounced destruction of the nuclei of the cells. The same length of exposure produced no change whatever in the skin. He found also that radiation of the abdominal wall for one hour with twenty milligrams of radium bromide caused pronounced destruction of the lymphocytes in the abdominal cavity. Gudzent investigated the effect on the spleen and other organs of injections of large doses of thorium X. The results were very similar to those produced by external radiations. According to this author, following the injections the entire spleen exhibits marked hyperemia. Its volume is later diminished. The cells of the spleen pulp decrease in numbers and in some places disappear altogether. On the other hand, the capsule and trabeculae are thickened and appear more prominent. Deposits of pigment are seen throughout the entire organ.

As to the change in the bone marrow, Thies found, in the experiments previously referred to, that in some cases, the marrow cavity of the bones was packed with erythrocytes while hemorrhages were common. In other cases, the bone marrow showed almost no cellular elements although an occasional polymorphonuclear or mononuclear cell was seen.

The favorable effects on the spleen and the blood picture, such as decrease in size of the spleen, decrease in leucocytes, etc., noted in cases of leukemia subsequent to radiations of the spleen, are referred to in a later chapter. In general it may be inferred from the experiments mentioned above as well as from a great deal of clinical evidence, that the spleen, lymphatic glands and bone marrow are extremely sensitive to radium radiations.

EFFECTS ON THE BLOOD

The blood either "in vivo" or "in vitro" may be affected by the rays.

Blood "in Vivo"

Only a few of the numerous experiments undertaken to determine the action of radium on the blood "in vivo" will be mentioned. Bouchard, Curie and Balthazard found that a marked decrease of the leucocytes occurred in mice which were made to inhale large quantities of radium emanation. Von Noorden and Falta found that inhalations of emanation caused primarily an increase of the leucocytes but later a decrease was sometimes noted. On the other hand, if a considerable quantity of emanation (100 mc. dissolved in 20 c.c. of normal salt solution) is injected subcutaneously no marked changes will occur in the blood (Price Jones, cited by Colwell and Russ). Brill and Zehner injected soluble radium salts subcutaneously into dogs. In one case, .184 mg. and in another case .064 mg. of radium chloride was used. They found that an increase both in the number of red cells and of leucocytes resulted. The effect of large doses was to decrease the number of leucocytes.

In the experiments of Thies, who irradiated white mice "in toto," a marked diminution in the number of leucocytes in the blood resulted. The polymorphonuclears were very scanty and the mononuclears were almost absent.

Aubertin and Delamosse found that radiations of animals produced a transient leucocytosis followed by a long continued leucopenia.

In a case of myelogenous leukemia, reported by Renon, Degrais and Thibaut, the splenic area was rayed although the spleen had been previously removed. Changes in the blood, such as diminution of leucocytes, etc., were produced that were practically identical with those found when the spleen is present and subjected to radiations. One may almost certainly conclude that these changes were due to the direct effects of the rays on the blood itself during its circulation through the abdominal cavity.

The effect on the blood of the internal administration of radium will be further considered in the chapter devoted to radium in internal medicine.

From the experiments already mentioned we may draw the following conclusions as to the effect of the rays on the blood:

Radium may affect the blood whether given internally or allowed to act externally.

As a result of the internal administration of radium or its derivatives, either by injections or inhalations, a pronounced effect may be produced on the blood and especially on the leucocytes. By this method of administration the whole organism and especially the hemopoietic organs receive a general though slight bombardment by the rays.

By means of external radiation of the whole body, or of the spleen especially, similar effects may be produced. The effect, in general, on the blood, of therapeutic doses acting internally or externally is to produce a leukopenia, which follows an initial transient leucocytosis.

The red blood cells and hemoglobin are frequently increased. While the exact mechanism of the action of radium on the blood is not thoroughly understood, it seems probable that the rays may act both directly on the elements of the circulating blood and also indirectly by affecting the hemopoietic organs.

Effect on Blood Coagulation

According to von den Velden, small therapeutic doses of radium internally cause the blood "in vivo" to coagulate more quickly. This result was noted in a case of hemophilia. The effect is only temporary. As the result of the administration of large doses of radium, causing a pronounced leucopenia, Kohom (cited by Gudzent) found that the blood coagulated more slowly. Von Domarus and Salle observed the same effects from large doses of thorium X.

Blood "in Vitro"

Blood "in vitro" may also be affected by exposing it to the radiations. According to Chambers and Russ, the red blood cells may be hemolyzed, especially by the alpha rays. Citrated blood exposed to radium emanation (.52 mc. per c.c.) was almost completely hemolyzed at the end of forty-eight hours.

According to the same authors, the phagocytic power of the leucocytes is reduced by exposure to the emanation, while prolonged exposure results in their complete disintegration. When blood serum is exposed to alpha rays, the properties of opsonin and hemolytic complement are lost.

Effects of the Rays on the Blood Vessels

The changes in the vessels that may be caused by radium rays have already been mentioned. Halkin, Thies, Horowitz and many others have described the changes produced in normal vessels. In general, the endothelium of blood vessels is extremely sensitive to radium rays. The endothelial cells swell up tremendously so that the lumen of the vessel may be obliterated. Later, degenerative changes take place and the cells disappear. The tunics of the vessels become infiltrated with leucocytes. Capillary hemorrhages may occur and later complete vascular obliteration may take place.

EFFECT OF THE RAYS ON CONNECTIVE TISSUE, MUSCLE AND CARTILAGE

Thies found that the white fibrous connective tissue, when exposed to the rays, underwent destruction. This effect was in direct contrast to the effect on the yellow elastic fibers which even after prolonged expo-

sures remained apparently intact. Dominici and Barcat confirmed the resistance of the yellow elastic fibers to the rays. According to the latter two authors, elastic fibers reappear in considerable proportion as a post radiation process. The smoothness and suppleness of the radiation scar is explained by this fact and also by the absence of excessive connective tissue formation in the scar.

Striated muscle degenerates under the action of the rays, the muscular fibers being replaced by connective tissue.

Hyaline cartilage may be initially destroyed but later there may be observed pronounced hypertrophic changes in the cartilage itself. The earlier observations of Thies on this point were later confirmed by Horowitz.

EFFECTS OF THE RAYS ON THE THYROID AND THYMUS GLANDS

No reports of purely experimental investigations as to the effect of radium rays on the thyroid and thymus glands have yet appeared. We may mention here the experiments of Krause and Ziegler and of Rave as to the effects of x-rays on the thyroid gland of animals. These authors did not detect either macroscopic or microscopic changes in the thyroid gland due to x-ray radiation. From a clinical point of view, however, very marked effects on the thyroid gland have followed x-ray exposures even though the tissue changes were negligible. The clinical effect of radium on the thyroid was shown first by Abbe and later by Dawson Turner, Aikens and many others. As a result of radiations with radium, the thyroid has been noted to decrease in size and functional disturbances have improved. This topic will be considered again under the discussion of the treatment of goiter.

The thymus gland in animals has been radiated experimentally with x-rays by Rudberg, Pigache and Beclére, Regaud et Cremieu and Eggers. In general it may be stated that atrophy of the organ occurs as a result of x-ray radiations. The excellent clinical results of Brayton and Heublein in producing atrophy of the pathologically enlarged thymus in children by means of radium radiations will be referred to in a later chapter.

EFFECTS OF THE RAYS ON THE STOMACH, LIVER, SALIVARY GLANDS, PANCREAS AND KIDNEYS

Delbet, Herrenschmidt and Mocquot performed gastrostomy on dogs and exposed the gastric mucosa to fifty milligrams of radium bromide, screened with 0.5 mm. of silver, for twenty-four hours. Hard beta and gamma rays were thus used, the latter preponderating. After a latent period of eight days, hyperemia and blood extravasation involving the

mucosa were noted in the irradiated area. Eight to fifteen days after the exposure marked destructive effects throughout the whole thickness of the mucosa were found. At the site of application of the radium, the superficial epithelial cells and the cells of the glands of the mucosa were destroyed. In the adjacent areas there were evidences of stimulation of these cells. The connective tissue of the mucosa and submucosa showed hyperplastic changes. No changes were observed except in a small area 3 cm. in diameter which was the site of the attachment of the radium tube to the stomach wall.

Thies, Horowitz and Mills have described the changes resulting from exposure of the liver to radium rays. Thies applied 20 mg. of radium bromide for six hours to the surgically exposed liver of a guinea pig. The radium was practically unscreened. Examined at intervals between the first and fourteenth day, the main histologic changes were early hyperemia and hemorrhages in the liver lobules, followed later by necrosis of the liver cells with separation and compression of the necrotic areas by newly formed connective tissue.

Horowitz exposed surgically the submaxillary gland and also the pancreas of rabbits and inserted 1 mg. of radium bromide unscreened. Local destruction of glandular tissue, followed by connective tissue repair, was noted. The same author used 20 mg. of radium bromide for experiments on the kidneys of rabbits. Inserted into the kidney for ten days, localized areas of necrosis were produced. Short radiations produced merely marked hyperemia.

EFFECTS OF THE RAYS ON THE TESTIS AND OVARY

Thies found that exposure of the testis of adult guinea pigs to 20 mg. of radium bromide for twenty-four hours resulted in destruction of the seminiferous epithelium. Fourteen days after exposure, no spermatozoa could be detected. Horowitz has confirmed Thies' experiments. Horowitz exposed the ovary of a rabbit to one mg. of radium bromide for ten days. This resulted in atrophy of the graafian follicles.

EFFECTS OF THE RAYS ON THE NERVOUS SYSTEM

Danysz exposed surgically the brains and spinal cords of mice, guinea pigs and rabbits and observed the effects of small amounts of radium (1 mg. radium salt) upon the central nervous system. Symptoms of paralysis, etc., appeared later and although no histologic changes were detected in the actual nerve elements, hemorrhages were noted. This observation led to the somewhat erroneous conclusion that the central nervous system was very easily affected by radium rays. Later Obersteiner, in many experiments on white mice, found marked inflammatory and degenerative changes in the vessels of the central nervous system.

He concluded that the symptoms of nerve derangement were fully accounted for by the vascular changes.

Horsley and Finzi experimented on the brains of monkeys. After trephining the skull, 55 mg. of radium bromide screened with 0.5 mm. of platinum and 1 mm. of rubber were placed on the brain substance and allowed to remain for two and one-half hours. The gamma rays were evidently responsible for the principal effects. No changes in either the nerve cells or the neuroglia could be made out at the end of twenty-six and thirty-one days, respectively. Marked vascular changes, however, such as thromboses and hemorrhages, were found. These authors also concluded that nerve tissue itself was relatively insensitive and that the vessel disturbance accounted for any nerve derangements.

As to the peripheral nerves, Okada and Scholtz found no alteration of the nerve substance after irradiating the sciatic nerves of rabbits. Horowitz, however, found in similar experiments, atrophic changes in the axis cylinders and destruction of the myelin sheath.

EFFECTS OF THE RAYS ON THE EYE

Birch-Hirschfeld studied the effects of 20 mg. of radium bromide when applied over the closed eyes of rabbits for periods of 4 to 6 hours. The effects were identical with those due to exposure to x-rays. After a latent period inflammatory changes appeared consisting of blepharitis, conjunctivitis, interstitial keratitis, and iritis. After several weeks these disturbances disappeared. Thirty-nine to 60 days after the exposures, retinal degeneration or optic atrophy or both effects occurred, differing according to the conditions of the experiments.

Certain physiologic optical effects may be referred to here. Hardy and Anderson have confirmed the earlier observations of Giesel and others as to certain optical effects of the radiations. The sensation of light produced in a dark room by bringing a radium preparation in front of the closed eyelid is due to the action of the gamma rays (the closed eyelid absorbing the beta rays) on the retina. The same effect is produced in the blind if the retina is intact.

The lens and retina of the eye are markedly phosphorescent upon exposure to both beta and gamma rays. If the phosphorescence of radium itself is obscured by black paper in a dark room, the open eye may still detect luminosity due, it is believed, to the phosphorescence produced in the eye ball.

Certain general conclusions may be deduced from a consideration of the observed effects of radium rays on vital tissues.

1. A latent period is always present after the application of radium. This period may last for several days or weeks. Histologic changes can be detected usually in a few days but clinical changes may be deferred

for 2 or 3 weeks. After exposure to beta rays (mixed with gamma) the latent period is shorter and signs of inflammation are more pronounced than when gamma rays alone are used. The use of considerable quantities of radium shortens the latent period.

2. Radium rays have a "selective" or as some would prefer to call it a "differential" action on vital cells. Colwell and Russ have suggested the term "selective absorption." The latter term suggests "that the more the rays are absorbed the greater the action they have." The physical evidence would indicate that two tissues of the same density will absorb the same quantity of gamma rays, while the clinical results in the two types of tissue of the same dose of rays may vary widely, depending on the sensitiveness of the cell to the rays. All cells may be influenced and modified and may even be destroyed by the rays if the dose is great enough.

As we have previously said, vascular endothelium is particularly sensitive to the rays. In tissues rich in vessels, therefore, there is little doubt that at least part of the effects observed are due to the action of the rays on the blood vessels. The sensitiveness of vascular tissue to radium rays accounts for the excellent results obtained in angiomata. Sometimes these tumors can be made to retrogress without macroscopic evidences of inflammation.

EFFECT ON BLOOD-MAKING ORGANS

The hematopoietic organs—spleen, lymphatic glands and bone marrow—are the most sensitive of all the tissues to the rays.

An important generalization as to the effect of x-rays has been made by Bergonié and Tribondeau. There is evidence to indicate that the same general law holds for radium rays. According to these authors, immature cells and cells that are actively dividing are more susceptible to x-rays than adult cells or cells that have already acquired the functional and anatomical characteristics of complete maturity.

THE METHOD OF ACTION OF RADIUM RAYS ON NORMAL CELLS

Various theories have been advanced to account for the changes in tissues that have been subjected to radiations. According to G. Schwarz, the radiations cause in the cells a chemical change, the main feature of which is the disintegration of lecithin. The lecithin theory, however, has not been confirmed by other researches. Wohlgemuth, Loewenthal and others have advanced the theory that the effect on the cell ferments is the essential factor in causing tissue changes. Later researches indicate that the radiations do not affect the ferments.

Ricker's theory, formulated as the result of his experimental studies

on the ear and kidney of the rabbit, is the following: As the result of the radiations the nerve supply of the blood vessels is first stimulated. This is followed by vascular dilatation and stasis. The cellular changes result from these effects. This theory neglects the fundamental studies of Hertwig which show that the nucleus of the cell is the first point of attack of the rays.

Another purely hypothetical suggestion, which is not supported by any experimental evidence, is that the plasmatic colloids of the skin are changed so that the ions of the surrounding medium enter into the cells and thus injure or destroy them. Gudzent has summed up our present knowledge of the nature and cause of the cellular changes produced by radiations as follows: "We may recognize both histologic and functional primary changes in irradiated cells. Histologically, the nucleus of the irradiated cell shows a 'foamy or honey-combed swelling.' In some cases there may be a shrinking and disintegration of the nucleus. The cytoplasm either shows no change at all or a slight 'foamy swelling' which may be secondary to the nuclear change. The more actively mitotic or reproductive the cell is, the more radiosensitive it is found to be.

"Heinecke called attention to the effect of the rays on certain highly radiosensitive cells such as lymphocytes and certain cells of the bone marrow. In these cells there was found to be practically no latent period after radiation. Within an hour after exposure to the rays, the nuclei of the lymphocytes showed signs of complete disintegration. This was shown by the presence of pycnotic globules and nodules which were attacked by phagocytes and in twenty-four hours disappeared almost completely. The same changes were observed in the cells of lymphosarcoma, which is also highly radiosensitive.

"One is forced to the conclusion that in these cases, at least, the essential primary effect of the rays is the direct action on the nucleus of the cell, causing its destruction. The cytoplasm of the cell is injured, also, but to a lesser degree.

"Functionally, the change in irradiated cells is shown by various experiments, such as those of Halberstaedter with reference to the effect of the radiations on trypanosomes and of von Wassermann on mouse carcinoma. These experiments tend to show that the primary functional change in the cells consists in the loss of their power of propagation. The nutritive powers of the cells are affected secondarily.

"We may thus conclude, in a word, that anatomically, the nucleus is the direct point of attack of the rays on the cell, and functionally, the reproductive power of the cell is the first to suffer. As to the ultimate nature or the exact character of the changes in the cell, we are still without adequate knowledge." This topic will be referred to again in the discussion of the changes in irradiated malignant cells.

EFFECTS OF THE DIFFERENT TYPES OF RAYS

Alpha Rays

The alpha rays, being practically always absorbed by the radium container, are never used therapeutically to the exclusion of the beta and gamma rays. Theoretically they could be employed by using *Radium F.* (polonium) as a source of the radiations inasmuch as this substance emits only alpha rays. According to Gudzent, the effect on the skin of radiations with polonium are similar to those observed after beta or gamma rays are allowed to act, i.e., an inflammatory skin reaction is produced. According to Becton and Russ, certain experiments done first with all the rays and then subsequently with the combined beta and gamma rays indicate that certain effects are due only to the alpha rays. Thus the disappearance of Altmann's granules in cells of healthy tissue is noted after using all the rays but this does not occur when beta and gamma rays are used. Gudzent states that by injections of thorium X, the organism is subjected mainly to an alpha ray effect. This topic will be considered again in a later chapter.

Beta Rays

In therapeutic applications in which the effect of the beta rays is especially desired, unscreened radium is applied to the tissues. Beta rays are always mixed, however, under these conditions, with gamma rays. Most of the experimental work undertaken to determine the action of the radiations on tissues has been done with mixed beta and gamma rays, although unfortunately the exact conditions of the experiments have not always been stated. As we have already shown in considering the subject of screens and filtration, varying portions of the beta rays may be employed depending on the thickness of the screens used.

Abbe deflected the beta rays by means of a strong magnet, and was thus able to use them alone unmixed with gamma rays. He achieved good results in various skin diseases. The practical difficulty in this procedure will probably prevent extensive use of this method, although it is interesting from a scientific standpoint. In the ordinary varnish or glazed plaques, devised for therapeutic applications, beta rays form about 90 per cent of the total radiation escaping from the instrument, when no screen is used. In applications lasting from several minutes to several hours, therefore, the effect of the beta rays greatly preponderates.

Gamma Rays

After filtering out the beta and some of the softer gamma rays by 2 mm. of lead the hard gamma rays alone act on the tissues. The experimental effects of these have been studied by a few authors and especially

by Dominici. The problem as to whether all three types of rays—alpha, beta, and gamma—have an identical effect on the tissues is not entirely settled. Colwell and Russ state that "different rays give rise to quite different effects upon one and the same variety of cell." Pappenheim, Plesch and Silva Mello, also, from their studies of the results of injections of thorium X, the effects of which are due largely to alpha rays, believe there is a difference between these effects and those of the beta and gamma rays. Heinecke, however, who subjected the entire organism of animals to x-ray exposures sees a great similarity in the biologic effects of thorium X and x-rays. In Heinecke's experiments with x-rays just as with injections of thorium X, the hematopoietic organs—spleen, lymphatic glands and bone marrow—were especially injured. All other organs were much less affected.

In an attempt to settle the problem of the identity of the biologic effects of alpha, beta and gamma rays, Gudzent and Levy carried out a series of comparative histologic examinations. The different organs, such as the spleen, bone marrow, lymph glands, liver and kidney of rats were sectioned, the animals having been killed by injections of thorium X, by roentgen rays, and by radium radiations, respectively. They concluded that the histologic effects of alpha, beta, and gamma rays were the same.

In contradistinction to some of the authors mentioned above, Gudzent, therefore, feels justified in assuming that the effect of the different rays depends solely upon the sensitiveness of the cells. The idea of an elective action of the different rays, by which each type of ray acts differently on the same cell, is thus not borne out. This author comes to the conclusion that the same explanation of the biologic effects of the rays may be given as for its physical and chemical effects. The radiated body, through ionization, becomes practically an electric field, which comprises the positively and negatively charged parts of the radiated material. In this ionization of the radiated tissues lies the explanation of the biologic effect of the rays.

From the clinical point of view it would appear to the writer that the same cells may react differently to different types of rays, in accordance with the belief of Colwell and Russ. Thus the angiomata, as a class, are very sensitive to both the beta and gamma rays from radium, sometimes yielding to doses that produce no visible inflammation. On the other hand, angiomata are not at all sensitive to x-rays yielding only to destructive doses with the latter agent.

Other examples, illustrating the different effects of different rays upon the same type of cell, might be cited but the full elucidation of this topic must await further investigations.

CHAPTER X

BIOLOGIC EFFECTS OF RADIUM RAYS (CONTINUED)

EFFECTS OF RADIUM RAYS ON MALIGNANT CELLS

Effects of the rays on rat and mice tumors. Certain tumors of rats and mice, it is well known, can ordinarily be transplanted from one animal to another by subcutaneous inoculation. These tumors afford, therefore, good material for experimental observations. The effects of the rays on these growths have been investigated by Apolant, Bashford, Murray and Cramer, Chambers and Russ, von Wassermann, Wedd and Russ, Wood and Prime and many others. It is possible to refer here to only a few of these experiments.

Apolant, who was one of the earliest investigators, found that radium applied to certain types of mice carcinoma "in vivo," i.e., in the body of the animal, caused the tumor to disappear in most cases and to diminish in size in others. As the result of histologic investigations, Apolant attributed the destruction of the tumor to the direct action of the rays on the cells. The connective tissue proliferation noted in the tumor was regarded as a secondary process.

Bashford, Murray and Cramer, in their experiments with Jensens mouse tumor, observed disappearance of the growths after radiations but did not detect any microscopic changes in the tumor cells. The marked connective tissue proliferation and frequent hemorrhages, noted by these authors, were regarded as the primary changes and the disappearance of the tumor cells was believed to be a secondary process.

Wedd and Russ and Chambers and Russ showed that portions of mice tumors if excised and exposed "in vitro," i.e., outside the body of the animal, to a sufficient dose of radium rays could no longer be inoculated successfully into other animals. Smaller doses checked but did not prevent the growth of the inoculated tumor. They concluded therefore, that the change or changes set up in the tumor cells themselves were responsible for the failure of the inoculated tumors to grow. The beta rays seemed to have a more powerful inhibitory effect on the tumor growth than the gamma rays.

Von Wassermann irradiated small pieces of mouse cancer "in vitro." In certain experiments the tumor retained its vitality when inoculated but did not develop. From this he concluded that while the rays acted directly on the tumor cells, they did not actually kill the cells but rather impaired their proliferating power. In other words, the rays acted chiefly on the propagating function and to a less extent on the nutritive function of the cell. This observation gave rise to the hypothesis that the actual

death of the cancer cells was brought about either by the natural aging of the cells or by the cytolytic powers of the organism itself. This view has not been generally accepted, however, most observers believing that the action of the rays on the tumor cell itself and especially on its nucleus is responsible for its death. This topic will be referred to again in a subsequent section when dealing with the question of immunity.

Wood and Prime have carried out a series of experiments to determine the action of the rays on certain rat and mice tumors. These authors have stated quite exactly the experimental conditions under which they worked with reference to (a) the amount of radium element used and the kind of container, (b) the screens, (c) the distance of the radium from the tissues, and (d) the length of exposures.

Tumor cells were exposed both outside and within the bodies of the animals to the action of the rays. Different types of tumors were used in the experiments. These included the Flexner-Jobling rat carcinoma, mouse carcinomata No. 11 and No. 180 of the Crocker Fund series and the Ehrlich spindle cell mouse sarcoma.

In one series of experiments, tumor tissue was excised and exposed outside the body of the animal to the radiations from capillary glass tubes containing 100, 83 and 17 mg. of radium element, respectively. As only the thin glass wall of the radium tube intervened between the radium and the tissue, practically all of the beta rays in addition to the gamma rays were effective. As proved by subsequent inoculation, the time required to kill the tumor cells was 10 minutes for both 100 and for 83 mg., and 20 minutes for 17 mg. The great destructive power of the softer beta rays was thus well illustrated.

In another series of experiments the tumor cells were also exposed outside of the body of the animal. The quantity of radium element contained in the glass tubes in the different experiments was 100, 83, 30, 20, 17 and 10 mg. respectively. The screening was 0.4 mm. of brass plus 0.65 mm. of glass. As this screening absorbed the alpha and softer beta rays, the hard beta mixed with gamma rays were effective. The distance was 1.05 mm. (0.4 + 0.65). The time required for a lethal dose for tumor cells under these conditions was 45 minutes with 100 mg., 60 minutes with 83 mg., 90 minutes with 30 mg., 150 minutes with 20 mg., 180 minutes with 17 mg., and 300 minutes with 10 mg.

In still another series of experiments the conditions were the same as in the last experiment but in order to filter out the beta rays and employ as far as possible pure gamma rays the screening was increased to 1.2 mm. of brass. In addition 5 mm. of filter paper were used between the tube and the tissues. This additional screening increased the distance of the radium from the tissues to 6.9 mm. Under these conditions, 100 mg. destroyed the tumor cells in 7 hours, 83 mg. in the same length of time, 30 mg. in 15 to 18 hours, 17 mg. in 20 hours and 10 mg. in 36

hours. In this last experiment it is seen that the time required for beta rays to kill tumor cells was approximately 6 to 8 times as long as that required for beta rays when mixed with gamma rays as described in the previous experiment. From this observation the authors concluded that there was a lack of sharpness in the lethal action of the gamma rays as compared with beta rays. It may be noted, however, that the distance of the radium from the tissues was about 6 times as great when gamma rays were used alone as when beta rays mixed with gamma rays were employed.

In still another series of experiments the authors used 83 mg. screened with 0.4 mm. brass, employing hard beta and gamma rays for 2 hours over a tumor "in vivo." Exposures longer than 2 hours were not given on account of the difficulty of further prolongation of the anesthetic. Upon subsequent inoculation into other animals, some slowing of growth was noted as compared with the controls, but the irradiated cells, even directly under the tube, were not killed. This failure was attributed to the fact that "in vivo," there was a supply of fresh nutriment to the cells. In addition any chemical products formed by the radium in the tissues were probably promptly removed. Tissue directly under the radium tube, but 1.1 cm. away from it, grew, when inoculated into other animals, as well or perhaps better than the controls. As the beta rays are absorbed by 1 cm. of tissue, this experiment apparently showed that the gamma rays from 83 mg. could not destroy cells "in vivo" in 2 hours, although "in vitro" such cells were destroyed in 1 hour.

The following are among the conclusions of the authors.

1. The hard beta rays, mixed with gamma rays, have about 8 times the lethal effect of the pure gamma rays on malignant cells. Inasmuch, however, as the beta rays are absorbed by 1 cm. of tissue, the gamma rays must be used for deep effects.

2. Sublethal exposures slow the growth of tumor cells for a certain length of time while still shorter treatments seem to stimulate the cellular activities.

3. The dose of radium rays required to destroy tumor cells "in vivo" is greater than that necessary to destroy isolated cellular elements.

This observation explains the fact that an exposure capable of destroying a small metastatic carcinoma nodule in man is quite ineffective in the case of a well vascularized primary carcinoma.

EFFECT OF THE RAYS ON HUMAN CARCINOMA

The clinical part of our work deals fully with this topic. It will be of interest, however, to mention here a few experiments which have been made to determine the dose of radium rays necessary to destroy human carcinoma.

F. C. Wood has made some investigations with reference to the effect

[illegible] rays on metastatic skin nodules in cancer of the female [illegible]es of 6 to 8 hours with 83 to 100 mg. of 1.2 mm. of brass and 5 mm. of filter paper, [illegible]rmanent disappearance of the nodules. [illegible]e rate of growth of the tumor cells but exposures or smaller quantities of radium had a stimulating effect on the cells. Dr. Henry Schmitz has also carried out a series of experiments to determine the effect of gamma rays in connection with recurrent breast cancers in the human body. He applied to carcinomatous nodules 50 mg. radium element, screened with 1.2 mm. of brass and placed at a distance of 1 cm. for periods varying from 4 to 13 or more hours. The distance of the nodules from the skin surface was carefully noted. After 10 days, various nodules were removed for microscopic examination. He concluded that carcinoma tissue within a distance of 1 cm. was destroyed by the gamma rays from 50 mg. of radium element after an application of about 12 hours, i.e., 600 milligram hours. The experiments of Kroenig and Friedrich, referred to in a subsequent chapter in which breast carcinoma was found to be about 1.15 times more susceptible to x-rays than the middle epidermal layer, are also of great interest.

ERRATUM

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Histologic Changes in Irradiated Malignant Tumors

We may now direct attention to the histologic changes that have been observed in irradiated malignant tumors. We shall mention also some of the various interpretations of these changes.

Extensive histologic observations have been made by Aschoff, Krönig and Gauss, Barcat, Bumm, Degrais and Bellot, Dominici, Ewing, Fauré-Beaulieu, Morson, Rubens-Duval, Schmitz, Wickham and Degrais and many others.

According to von Hansemann and Schottlaender, nothing is to be seen histologically in irradiated tumor tissue that might not also be observed in rapidly growing and disintegrating nonirradiated tumors. Ewing, on the other hand, states that "the series of morphologic changes which take place after successful radium application is specific and that when these changes are present in undisturbed course it is possible to recognize tumor tissue treated by radium."

According to Dominici and Rubens-Duval, radium rays act upon carcinoma cells in two different ways. By one method, the cells are killed outright, without any histologic change occurring that can be detected. By another method, definite histologic changes occur and can be observed prior to the death of the cell. These changes consist of nuclear hypertrophy and budding; hypertrophy of the cell body; an increase in the number and size of the so-called "pseudoparasitic" bodies. In the case of squamous-cell carcinoma, as of the lip, keratinization may accompany the above changes.

These authors believe that while some of the cancer cells are destroyed by the rays, others simply have their powers of proliferation arrested. Other authors subsequently expressed the same belief.

Bumm has reported a case of inoperable carcinoma of the uterus in which surgical operation was performed after intense radiation of the tumor. During the operation, carcinomatous nodules were observed outside of the operation field. Fifteen months afterward, however, the patient was in good health. Bumm suggested that these outlying cancer cells were damaged so that they could not proliferate although histologically the damage could not be detected. Subsequently, in a study of the morphologic appearance of cancer clinically cured by radium and x-rays, Levin and Joseph cited several cases in which clinical arrest of malignancy was apparently brought about by radium radiations, although no morphologic change in the tumor cells could be detected. These authors also suggested that the first effect of the rays probably was to inhibit the proliferating power of the cells. Cell degeneration and death thus occurred, not as the direct result of the action of the rays, but in the natural course of the life cycle of the cancer cell.

The view that radiation may, so to speak, have a sterilizing effect on the cancer cells and inhibit their proliferating power without directly killing them receives some support from the investigations of von Wassermann on mouse cancer. These experiments have already been referred to.

Ewing has given the following description of the histologic changes occurring in irradiated epidermoid carcinoma of the cervix. "Within from three to five days after the application in the cervical canal of 300 mc. of radium emanation in a platinum tube, there is hyperemia of the tissues, beginning exudation of the lymphocytes and polymorphonuclear leucocytes and swelling of all the cells.

"In the second week, the cords of tumor cells present a characteristic appearance. The nuclei are swollen, homogeneous and hyperchromatic. The cell bodies are enlarged, the cells loosened, hydropic vacuoles appear in the cytoplasm and fusion giant cells form.

"In the third week, the number of cells is greatly reduced. Many appear to suffer liquefaction necrosis. Others are invaded and mechanically broken up or compressed by lymphocytes and proliferating stroma.

"From the fourth to the fifth weeks only pycnotic nuclear fragments or an occasional giant cell are visible or no traces whatever remain. Meantime the stroma has been active and appears to take an active part in the process. Leucocytes become overabundant, the capillaries proliferate actively and the stroma is transformed into granulation tissue in which numerous new capillaries penetrate and excavate the tumor cell nests. The gathering of leucocytes, lymphocytes, plasma cells and polyblasts in the later stages of radium reaction may be extremely profuse and in this respect the reaction is somewhat specific.

"Eventually the site of the tumor is occupied by granulation tissue from which slight serous and cellular exudate is discharged. Later epithelium grows over the denuded surface, completing the repair.

"All manner of variations occur in the reaction of tumor tissue to radium. Complete simple necrosis follows over action of radium. Bulky tumors may present large areas of simple necrosis in which cysts form by liquefaction. The stroma as well as the tumor may be destroyed in which event extensive scarring will result. In the foregoing scheme of changes it would appear that just enough radium had been employed to cause slow degeneration of tumor cells and stimulate regenerative growth of granulation tissue."

Morson imbedded radium, contained in a platinum tube, in the substance of carcinomata, allowing the tube to remain for periods of from 15 to 24 hours. The thickness of the wall of the tube was such that only the gamma rays were effective. Sections of the irradiated growths were examined at various intervals after the exposure. In some cases, histologic changes, consisting of nuclear irregularity and fragmentation, could be detected in the cancer cells, especially in those adjacent to the tube, as early as 15 hours after the commencement of the exposure. In certain cases, 48 hours from the commencement of the exposure, sections showed cancer cells in different stages of degeneration lying in a disorganized mass of tissue. In many cases, 14 days after the exposure, there were no evidences of carcinoma cells. In other cases, however, carcinoma cells could still be detected at the end of 2 months. These cells, nevertheless, showed degenerative changes, such as enlarged nuclear and vacuolated cytoplasm, while they were encircled by dense connective tissue.

Gudzent says: "In the histologic changes due to the radiations, we must place in the foreground the injury and destruction of the nucleus of the carcinoma-cells. According to the investigations of Grasnick on embryonal tissue, we must assume that in the nuclei which are undergoing mitotic changes the effect takes place immediately after the radiation and without any latency. These injuries are not disclosed however until a latent period of several days has elapsed. In the completed stage, all signs of the disintegration of the nuclei can be observed, such as decrease of the staining power, swelling with vacuol-formation, and shrinking and dissolution. The injury to the nuclei undoubtedly causes the death of the cells. To what extent the cell plasma is injured, is not as yet known, but one can observe that the cells decrease in numbers and finally disappear. In addition to these primary changes, others manifest themselves which are of far-reaching importance in the curative process. Very soon after the first injury to the nucleus and the cell makes its appearance, extensive proliferation of the connective tissue sets in. One observes the young connective tissue permeating the swell-

ing in all directions. This connective tissue breaks open the cell complexes of the parenchyma, encircles single complexes, pressing them together and strangling them. Sometimes cells with several nuclei are formed. Klein and Duerk have called these 'conglutinal giant cells.' These exhibit a lessened power of growth and diminished vitality. One is led to infer that the connective tissue is actively combating the carcinoma cell, limiting and even destroying its vital processes. In a later stage, the connective tissue shows signs of maturity; the number of cells is diminished, while the connective tissue fibers coalesce and become sclerotic. The cause of the new formation of connective tissue may be found in the effect of the radiation. We must assume, then, that the same amount of radiation which causes the disintegration of the cells, has a stimulating effect on the connective tissue cells. This assumption is very hard to bring into harmony with the researches of Root. This author found the fixed connective tissue cells very radiosensitive. To regard the new formation of connective tissue as a reaction which serves as an intermediate substance for interstitial spaces cannot be accepted for the reason that it proliferates very early and in its later stages especially shows various signs of the influence of the radiation. In all probability both assumed causes play some part in this, but this must be cleared up through future research.

"In connection with this connective tissue proliferation, the injury and destruction of the blood capillaries, whose radiosensibility is well known, must be considered. Thus the hemorrhages occurring soon after radiation are explained. It seems to be clear that the interruption of the blood supply causes severe injury to the carcinoma cells. In the later stages, proliferation and new formation of capillaries set in. These accompany especially the newly formed connective tissue bundles. Between the cell bundles of the parenchyma and those of the supporting tissue, cells of hematogenous origin, leucocytes, lymphocytes and so-called leucocytoides, can be observed, at a certain stage. According to Klein and Duerk, the fragmentary nucleated leucocytes especially seem to have the important rôle of removing the cell particles which have been destroyed. It can be seen that these cells, like phagocytes, cling to the protoplasmic bodies which are more or less isolated from their epithelial cell complexes, and practically gnaw off fragments here and there, so that a concave shaped loss of substance can be noticed. Sometimes single epithelial cells are densely covered by these phagocytes, which undoubtedly are hard at work causing their reduction and dissolution. This phagocytic process is to be regarded as secondary and provoked by the dissolution of the radiated cells.

"If the destruction of all carcinomatous cells has been attained, the connective tissue completely fills up the interstitial spaces. In due time it matures, becoming poor in cells and more sclerotic than the con-

nective tissue which fills up interstitial spaces caused by other conditions."

Dominici has given the following description of the histologic changes occurring after radium treatment in a very vascular myeloid sarcoma. From the commencement of the treatment to the complete disappearance of the growth there elapsed a period of a little over 4 months. It is noteworthy that Dominici inferred from his studies that not merely were the malignant cells destroyed by the action of the rays and replaced by fibrous tissue, but a peculiar evolutionary process was set up in the sarcoma cells themselves, so that they became, at least in part, converted into cells indistinguishable from normal connective tissue. The nuclei of the sarcoma cells became more spindle shaped. Atrophic changes could also be made out. The protoplasm of the giant and sarcoma cells became replaced by connective tissue fibers which Dominici believed arose from the alteration of the protoplasm itself. Adjacent to the nuclei, however, a portion of the protoplasm remained intact. This unaltered protoplasm formed, with the nuclei, typical connective tissue cells. The processes just described occurred throughout the growth. The lumen of the blood vessels became smaller so that they appeared like capillaries lying in the midst of fibrous tissue. It seemed that the malignant sarcoma cells were transformed into fibrous cells. The fibroma-like structure remained stationary or became smaller, showing no tendency to increase as in ordinary fibromata. The arrangement of the connective tissue fibers was remarkably regular.

THE METHOD OF ACTION OF RADIUM RAYS ON MALIGNANT CELLS

While there has been much speculation as to the mechanism of the action of radium rays on malignant cells, little is definitely known. The changes to be observed histologically do not differ from those already described as occurring in normal cells. The same theories of the action of the rays which have been referred to in the previous chapter have also been advanced to explain the morphologic and functional change in malignant cells. As yet, however, no explanation has been made that is entirely satisfying and indeed none is likely to be made until our knowledge of intracellular metabolism is complete.

According to Ewing "it is a reasonable assumption that the gamma rays while traversing the tissues give rise to secondary beta rays, electrons, which act on the cells. That the action is electrical, accelerating cell ferments, ionizing gases, altering lipoid emulsions, etc., may be conceived but is not demonstrated. These questions may well serve to stimulate and aid in the study of the physics, chemistry, and finer morphology of the cell.

"Interpreted from the pathologic standpoint, the observed changes in cell morphology indicate an action directly on the tumor cell and especially on its nuclear mechanism, with profound and progressive chemical changes in the nuclear proteins, attended by the formation of acid products and by the absorption of material, probably water. The appearance of the cell cytoplasm suggests hydrolytic cleavage of cell proteins and these seem to excite leucocytic emigration.

"The growth of capillaries may be explained as a regenerative process following a loss of tissue equilibrium, or it may involve a direct stimulating action of the radium on endothelium and fibroblasts. In any event the process is very complex and in many cases there are strong hints at a restoration of normal resistance of the connective tissue against lawlessly proliferating tumor cells."

Summing up the various findings and interpretations, the available evidence merely suggests the probability that some kind of an intracellular and especially an intranuclear chemical change is produced by the action of radium rays on malignant cells. The exact nature of this change still remains a secret. The nucleus of the cell is injured first and this injury is attended by the loss of the power of mitosis. As a rule malignant cells are much more susceptible to irradiations than the cells of most normal tissues. This peculiar sensitiveness forms the foundation of radium therapy in malignancy.

THE QUESTION OF STIMULATION OF TUMOR GROWTH BY INSUFFICIENT RADIATION

According to some authors, radiations that fail to kill the tumor cells may even stimulate their activity and cause increased tumor growth. This is a problem of the greatest importance and one about which there is much difference of opinion. Wood and Prime thought that certain mouse tumors treated with radium and then inoculated into other animals grew more rapidly than the controls. Ewing remarks, however, that "their results were quite inconstant, and the extirpation of the exposed cells removed them from the attack of lymphocytes and granulation tissue, which are the main agents of tumor destruction set to work in the curative process excited by radium."

Reference may also be made to the experiments of Hastings, MacCormac and Woodman. These authors exposed cancerous skin nodules, secondary to mammary carcinoma, to the radiations from pitchblende. This mineral contains several radioactive bodies, but the radiations from a given quantity are at least a million times weaker than those from the same quantity of radium. One might infer, therefore, that malignant cells would probably be stimulated by exposure to pitchblende rays on the assumption of inadequate dosage. The treated carcinomatous skin nodules, however, showed no recognizable clinical differences from

the untreated nodules after the lapse of several months. Histologically the treated nodules disclosed evidences of the effect of even these weak radiations. Nuclear changes in the cancer cells occurred, the principal change observed consisting of the partial disappearance of chromatin which was at the same time condensed about the nuclear membrane. In addition, delicate connective tissue fibrils appeared between the cancer cells so that they became separated into small aggregations.

We may refer also to the studies of A. and O. Hertwig. These authors have shown that mitosis of cells is inhibited by radiations of even the weakest intensity.

From the clinical side, many observers, including the writer, have not been able to convince themselves of an actual stimulation of tumor growth by radium rays. One may doubt if such stimulation occurs under the modern method of very large primary doses. If it could be shown conclusively to occur it would constitute one of the many limitations of radium treatment to be guarded against as far as possible by powerful radiations directed especially toward the periphery of tumors. One should not forget, however, that very massive treatments with heavily screened radium may even defeat their own object by causing such extensive injury to normal tissues as to result in serious harm to the patient. This fact tends to limit the usefulness of radium in the treatment of very extensive and deeply situated cancerous masses.

The Problem of Immunity

It would be beyond the scope of this work to consider in detail the complex problem of immunity to malignant tumors. Tyzzer has recently published a résumé of the subject and the reader may be referred to his monograph. Additional references will also be found in the bibliography. A few experiments that bear on the production of immunity by radiations with radium may be referred to. Contamin was apparently the first to show that if cancer cells were irradiated for a short time with radium or x-rays and were subsequently inoculated into mice a degree of immunity was produced. He also observed that an excessive exposure to x-rays destroyed the immunity conferring power of the cells. Wedd, Morson and Russ confirmed the general trend of these observations. These authors irradiated "in vitro" tissues from the Twort tumor (adenocarcinoma) with a measured dose of beta rays. The radiation was sufficient to prevent the formation of growing tumors when the radiated tissue was reinoculated into mice although the tissue, after persisting for several days, was absorbed. Some days later the animals were inoculated with the usual strain of tumor tissue which had not been irradiated. As the second graft of tissue did not develop, an immune condition of the animal was inferred. By gradually increasing the length of exposure, it was found that a

point was reached at which the irradiated tissue when inoculated no longer conferred immunity. These authors also found that if normal and radiated tumor cells were inoculated simultaneously no immunity was produced. In commenting on these experiments, Colwell and Russ, while recognizing that no generalization can be made on account of the limited number of the experiments, state that "excessive irradiation of a tumor may therefore very easily abolish any immunity that the absorption of irradiated cells may be capable of giving rise to. It would appear that the best condition for producing immunity is for the cells to receive an exposure that will insure their gradual degeneration and disappearance."

It has been asserted by some clinicians that the irradiation of a tumor such as a breast cancer may cause not only the irradiated tumor but also distant metastases such as axillary nodules to shrink.

In order to explain this alleged effect, the hypothesis has been advanced that substances are set free from the irradiated growth which act on the secondary deposits of the tumor. Rohdenburg and Bullock have shown however that an established transplanted tumor, i.e., one that has excited a stroma reaction and obtained a blood supply, is not susceptible, even though radiumized, to immunity reactions. They have pointed out that it is much less likely, therefore, that an unradiumized tumor is in any way sensitive to the immunity process. It is probable, therefore, as these authors state, that the disappearance of tumors—if they really do disappear—situated at a distance from the radiated growth is due to some other process than the influence of substances set free by radiation. If the shrinkage of such tumors really occurs, it may be due to the disappearance of inflammatory edema in the nodules and the destruction of lymphoid elements which are very sensitive to radiation.

The writer would take sides with those who doubt the probability of any effect of radiation on tumor deposits outside of the field of radiation. So far as our observation goes, radiumization of a tumor has no effect whatever on metastatic deposits in other parts of the body.

Rohdenburg and Bullock have also pointed out that the problem of immunization and cure of animal tumors on the one hand and of human tumors on the other is a very different one and that the results so far achieved in developing immunity in animals cannot be transferred to man.

In man, the problem is to cure or produce immunity against a spontaneous tumor.

In animals, immunity has only been produced against transplanted tumors. According to these authors, an animal cannot be immunized against its own tumor.

The following observations of Murphy and Norton bear on the problem of the nature of the immunity process. While the experiments of these

authors have evoked great interest, it must be said that they have not been completely confirmed. Sittenfield's experiments, e.g., do not support their conclusions as to the importance of the lymphocyte in the defensive mechanism of the organism.

Murphy and Norton, in their investigations of the effect of x-rays on the resistance to cancer in mice, have apparently shown that the resistance to heteroplastic tissue depends on the activity of the lymphocytes. The chick embryo normally lacks the ability to destroy a heteroplastic tissue graft. If a small amount of lymphoid tissue from an adult is supplied, it becomes as resistant as the adult. On the other hand, if an adult animal has the main part of its lymphoid system destroyed by repeated x-ray radiations, it loses the power of destroying a graft of heteroplastic tissue. Histologically, the main characteristic of a failing heteroplastic graft is a marked local accumulation of lymphocytes. The same histologic picture is seen in a failing cancer graft in an immune animal of the same species. Simultaneously with the production of the cancer immunity and while the lymphocytes are accumulating around the cancer graft, a lymphocytic crisis occurs in the circulating blood. This crisis is lacking in animals susceptible to the cancer graft. It has been noted that while repeated small doses of x-rays will destroy the lymphoid elements of an animal, one small dose will stimulate it and cause a lymphocytosis. Bearing in mind these facts, which had previously been demonstrated, the authors studied the relation of the resistance of mice to their own spontaneous tumors. Among their experiments, all of which were carried out with suitable controls, were the following: The cancer was removed by operation from the animal. The animal was then given a stimulating dose of x-rays. Immediately afterward, a graft of the original tumor was placed in the groin of the animal. In a series of 52 animals so treated, 50 per cent were rendered immune to their own cancer and in the other 50 per cent the return of the disease at the operation site was greatly retarded. The authors suggest that if one dose of x-rays causes this effect, a more pronounced effect might be caused by a second stimulating dose at a subsequent time.

The foregoing experiments have a special interest in connection with the frequent clinical observation that malignant tumors in humans respond differently to radiation, some being easily affected while others, of apparently the same type, are much more resistant. It may be possible that the different response of similar tumors to radiations depends to some extent upon the systemic defensive powers of the organism. It would appear from these experiments that while the radiosensibility of the tumor cells is probably the chief factor, the lymphocytic system is also of some importance in connection with the disappearance of malignant growths under the influence of the radiations. An important practical lesson may be drawn from these experiments. In cases de-

manding powerful radiations, frequent observations of the leucocytes should be made. A marked reduction in the number of leucocytes is a signal for caution in proceeding with further treatments until the leucocyte count is improved. When the spleen, lymphatic glands and bone marrow, which are especially radiosensitive, are likely to receive heavy doses either intentionally or incidentally in the course of the treatment, it is particularly necessary to proceed with care.

CHAPTER XI

THE RADIUM REACTION

Broadly speaking, all of the biologic effects of radioactive substances when applied externally or introduced into the organism are due to the radiations and are manifested by various disturbances which may be termed reactions.

In this chapter we shall consider only the biologic effect, i.e., the reaction due either to (1) surface radiations or to (2) the introduction of radioactive material into tumors. The effects of radioactive material administered by mouth or introduced intravenously or subcutaneously will be discussed in the chapter on radium in internal medicine.

1. SURFACE RADIATIONS

These are radiations that are used on the surface of the skin. They may produce (a) a constitutional reaction or (b) a local reaction.

(a) Constitutional Reaction Due to Surface Radiations

In patients who have received relatively large doses such as may be delivered by 250 milligrams of heavily screened radium applied for fifteen hours or more, nausea and vomiting, a feeling of depression and even prostration may occur toward the end of the treatment or after the radium is removed. A metallic taste is often complained of. These symptoms usually pass off within twenty-four hours. In some instances they may last for weeks. Elevation of temperature during or subsequent to such an exposure is unusual in our experience although this phenomenon has been described by some authors. In using less intense doses of surface radiations such as may be given for a small epithelioma of the skin, no constitutional effects are ordinarily observed.

(b) Local Reaction Due to Surface Radiations

Wickham and Degrais were the first to point out that important modifications of vital tissue such as resolution of a tumor may be caused by the surface application of the rays without the supervention of visible inflammation. Hence, they called this action of the rays a "selective action." Later this term was used to indicate that the rays affect certain types of cells in a "selective manner" regardless of the presence or absence of macroscopic inflammation. Inasmuch as all vital tissue may be affected to some extent, the term "differential action" has been proposed by other authors to indicate the fact that the rays affect some tissues

more markedly than others. Colwell and Russ have suggested that the thing irradiated is of as much importance as the rays and have proposed the term "selective absorption." This term implies that certain tissues absorb more rays than others. Hence "the more the rays are absorbed the more the tissues are affected."

It is difficult to express in a single term both the complex action of the rays and the response of the tissues.

It would appear that the rays have a "selective" or "differential" action on vital tissue. This expression means that the rays affect certain normal tissues such as the spleen and lymphatic glands more readily than others such as connective and elastic tissue. The rays also affect certain tumors such as lymphosarcomata much more readily than some other types of new growth, such as squamous cell epithelioma.

This "selective action" of the rays makes possible radium therapy in malignancy for experience has shown that many types of malignant tissue are more readily affected than most normal tissues.

On the other hand, the response of the tissues to the action of the rays may perhaps best be indicated by the terms "selective reaction" and "inflammatory reaction."

By "selective reaction" it is meant that under the influence of radium rays abnormal tissues may undergo a retrograde metamorphosis without visible inflammatory changes. This reaction is illustrated by the response to radiation of certain epitheliomata, keloids and angiomata which may sometimes retrogress and disappear without visible inflammation.

By the term, "inflammatory reaction" we designate the ordinary changes characteristic of inflammation which may easily be produced by radium. Inflammatory reaction usually appears between the seventh and fifteenth day, but it may appear as early as two or three days after exposure, and in some cases it may be delayed for as long a period as four weeks.

For convenience, four degrees of "inflammatory reaction" may be distinguished, although these degrees or stages of reaction pass insensibly into each other. These are, first—simple erythema; second—erythema followed by desquamation; third—vesication or superficial ulceration; fourth—deep ulceration.

We may now describe the clinical effects of radium rays upon the skin and mucous membranes when doses sufficiently intense to produce inflammation with superficial destruction are used.

After the application of radium to the healthy or noninflamed pathologic skin, there is a latent period during which no apparent effect is seen. The duration of the latent period depends upon the amount of radium used, i.e., upon the intensity of the rays; the type of rays, i.e., whether beta or gamma rays preponderate; and to some extent upon the sensitiveness of the tissues. If a one-fourth strength glazed applicator containing about 20 mg. of radium element is applied unscreened directly

to the skin for one or two hours, the latent period is very short—sometimes not over twelve to thirty-six hours. The beta rays form about 90 per cent and the gamma rays about 10 per cent of the total radiation from the apparatus used in this manner. If the same apparatus is screened with 2 mm. of lead so that only the hard gamma rays are effective and is applied at a distance of 1 cm. for thirty hours the latent period may last for from seven to fifteen days. Speaking very generally, the larger the quantity of radium and the more the beta rays preponderate, the shorter the latent period is found to be. The first evidences of the inflammatory reaction are slight redness and swelling of the skin which itches and becomes tender. A crust of yellowish or greenish gray aspect then gradually forms. Vesicles or bullæ may occasionally precede the formation of the crust. The tissues underneath the crust may be dry or moist depending on the degree of the reaction. The crust may last for days or weeks, sometimes falling off or being accidentally knocked off but usually reforming several times before healing occurs. The general appearance of a well-developed crust has been compared to that of impetigo contagiosa. If the crust has rested on an ulcerated and suppurating base it becomes more and more dry as the inflammation subsides. Frequently the different layers of crust become superimposed so that a mass of dried detritus, several millimeters thick and of characteristic "oyster shell" appearance results. Finally the crust may be detached "en masse" leaving a smooth, supple, white and hairless surface. The duration of inflammatory reaction may vary within the widest limits. Reactions of the first and second degree may apparently subside in from one to four weeks. A moderately severe reaction of the third degree requires a period of from six to eight weeks for complete recovery. If a severe reaction of the fourth degree has been produced, six or eight months or even a longer time may elapse before healing occurs. In some cases, if the reaction has been of considerable severity, attacks of dermatitis (so-called secondary or deferred reactions) may occur at intervals for several years, even after complete healing has apparently taken place.

Fortunately a tendency to the development of epithelioma on the scar tissue resulting from severe radium reactions has not been observed. Telangiectasia frequently supervenes on the radium scar in the course of eight or ten months after healing has occurred.

In the treatment of inflammatory skin reactions the writer has found the following application of some benefit in relieving the subjective symptoms: Zinci oxidi, 5; bismuthi subnitratis, 5; adipis lanae hyd., 12; ol. olivae, 60; aq. calcis, 60. Irritating applications should be avoided. In fact, in many cases it is best to make no local applications, but to expose the inflamed area to the air and allow nothing, not even gauze dressing, to come in contact with it.

When radium is applied to the mucous membrane in sufficient doses an appearance is produced at the end of the latent period not unlike that caused by the application of nitrate of silver. The irradiated area becomes at first white and later yellowish white. At the height of a reaction of moderate degree, a more or less dense, yellowish white, adherent membrane covers the treated area, which is surrounded by a narrow red zone of inflammation. This membrane gradually becomes exfoliated and is replaced by epithelium which grows in from the edges. A smooth and supple scar is usually left which is whiter than the normal mucous membrane. Some months later, telangiectasia may occur.

Secondary or deferred reactions have not received the attention that their importance warrants. They may appear several months or even several years after the primary reaction has healed. They usually come on suddenly, i.e., they develop quite fully in the course of a few days. In some cases of epithelioma of the mucous membranes it may be difficult to determine whether a deferred reaction or a recurrence of the growth is present. The mucous membrane, if affected by a secondary reaction, becomes grayish white and in a few days is covered with an adherent membrane. A condition practically identical with that observed during the primary reaction develops. Secondary reactions may persist for weeks or months. Sooner or later, however, healing occurs in almost all cases.

In a patient with a pelvic periosteal sarcoma that was treated with very large doses, a severe primary reaction of the skin of the abdomen developed which persisted for nearly eight months. Two years later, upon the site of the former area of reaction, a secondary reaction developed spontaneously. This reaction which took the form of a superficial ulceration accompanied by the formation of a pultaceous adherent mass of necrotic tissue, required three months for healing.

In the therapeutic application of radium, severe reactions should be avoided when possible. In the treatment of certain dermatological conditions, however, conservative use may be made of the destructive action of radium. In producing reactions intentionally for cosmetic purposes, we always employ the glazed plaques. In tissues that have been subjected to previous treatment such as by x-rays, cauterization, etc., a radium reaction is likely to be atypical and healing may be deferred for months. Such tissues should be treated with the greatest caution and not more than one fourth of the normal dose should be given.

Areas that have been treated with radium may be sensitive to temperature changes long after healing has occurred. Many patients complain also of a peculiar sensation as if ants were crawling on the skin. All of these symptoms usually disappear in the course of a few months but they may in exceptional instances last for years.

2. INTRATUMORAL RADIATION

Local Reaction Due to Intratumoral Radiations

In certain cases, as we shall describe in a subsequent chapter, radium salts or radium emanation may be introduced directly into the substance of tumors—"intratumoral radiation." Under these circumstances the radioactive material is usually enclosed in metal or glass containers—i.e., needles or ampoules. The changes in the tissues caused by the insertion of minute glass emanation ampoules have been investigated by Halsey J. Bagg. A résumé of some of the results of these studies may be conveniently given at this point.

A series of emanation ampoules or tubes was buried in normal rat tissue of different kinds—skin, muscle, brain, testes, etc. Another series of tubes was buried in the Flexner-Jobling rat carcinoma. Still another series of tubes was imbedded in human carcinoma. Suitable control experiments, undertaken to prove that the glass itself was not responsible for the effects, were made by imbedding nonactive emanation tubes in living tissue. Among the conclusions arrived at by Bagg were the following: In rat carcinoma, definite histologic changes were noted two days after the tubes were buried. Definite radium effects, such as complete necrosis around the tubes and changes in the adjacent outlying cells, were noted seven days after the tubes were inserted. Complete recovery in the case of a transplanted rat carcinoma two cm. in diameter was noted, about forty-two days after the insertion of three tubes containing 3 mc. each, placed 1 cm. apart and about 5 mm. below the surface.

Lethal effects on normal tumor cells were produced by relatively small doses of emanation, less than one mc. per tube being a satisfactory dose.

An area of tissue about one cm. in diameter was effectively radiated by each tube.

Histologically, the main effect was the production of an area of necrosis which was surrounded by a pronounced leucocytic infiltration. The area of effectively radiated tissue did not increase in direct proportion to the amount of emanation in the tube. When relatively strong tubes were used, the tissues in close proximity were radiated for a longer time than was necessary to produce lethal effects in these cells. The rays did not penetrate effectively, however, to a much greater distance than the 1 cm. zone, probably because the easily absorbable beta rays were responsible for the main effects. While the gamma ray effects from relatively strong tubes are undoubtedly greater than those from the weaker tubes, it was difficult to determine this point because of the prompt reduction in size of the treated tumors. Bagg suggests that human tumor tissue may be treated most effectively by imbedding tubes of 0.5 mc. strength 1 cm. apart evenly throughout the mass.

Biologic Hypersensitiveness

There is little doubt that some individuals are more sensitive to radiations than others. In certain individuals, prolonged exposures with a considerable quantity of heavily screened radium will cause marked constitutional effects such as nausea and depression. In others, a similar exposure produces little or no constitutional effect. Certain types of skin are apparently quite radiosensitive and may react severely to an exposure that will cause little or no effect in other types. We recognize only a few of the conditions that render one skin more radiosensitive than another. Among these conditions are (1) a lack of the normal quantity of pigment indicated by the fair color of the skin; (2) absence of the normal seborrheic oiliness. These factors seem to render the skin more radiosensitive. Certain parts of the integument in the same individual are also more radiosensitive than others. In general, the mucous membrane is more sensitive than the integument. Marked idiosyncrasies, however, are relatively rare but should always be thought of in the beginning of a course of radiations.

CHAPTER XII

THERAPEUTIC APPARATUS

In the treatment of disease, radium may be applied in the form of (a) radium salts, (b) radium emanation, or (c) active deposit.

The therapeutic effects of radiations from apparatus containing radium salts, radium emanation, or active deposit are identical.

A. APPARATUS CONTAINING RADIUM SALTS

Radium salts may be placed for therapeutic use in (1) tubes, (2) needles, (3) flat plates or plaques.

1. **Radium Tubes.**—Radium tubes are made of capillary glass and are filled usually with from 5 to 50 mg. of radium element in the form of sulphate. This is closely packed so that the salt does not move about in the tube. The length of the tubes varies from 1 to 2 cm. and the diameter

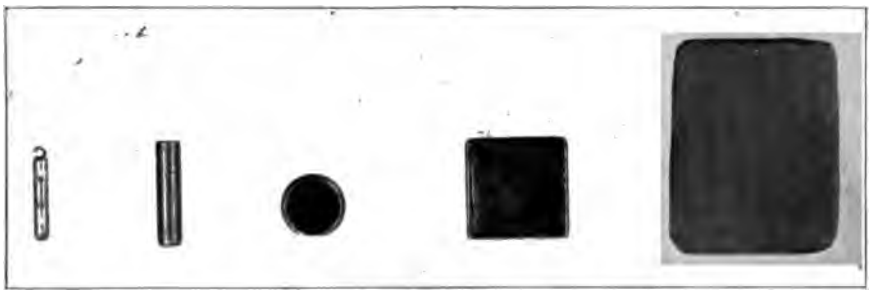


Fig. 19.—Apparatus for the application of radium.

A, Silver tube containing 15.21 mg. radium element. Length of tube 16 mm., outside diameter 2 mm., wall thickness $\frac{5}{10}$ mm. *B*, Brass screen, wall thickness 1 mm., to contain tube *A*. *C*, Round glazed applicator, ½ strength, 1 cm. in diameter. *D*, Square glazed applicator, ¼ strength, 2 by 2 cm. *E*, "Toile" wrapped in rubber dam, $\frac{1}{20}$ strength, 3 by 4 cm.

from 1.5 to 3 millimeters. For convenience and safety in handling, the capillary glass tubes are usually inserted into silver tubes, just large enough to contain them. The silver tube may have a small screw cap to retain the glass tube and may be hermetically sealed. The wall thickness of the silver tube is usually $\frac{5}{10}$ mm. but it may be of any desired thickness or the tube may be made of platinum or any other material.

Over these tubes may be slipped screens of different thicknesses in order to filter out varying portions of the beta and gamma rays.

2. **Radium Needles,** instead of the ordinary tubes, may be used and introduced directly into the tumor tissue. In this type of apparatus the radium sulphate is packed directly into a hollow needle which is fitted with a fine screw cap containing the eye of the needle. The cap is soldered

on so that the radium may be completely protected. As much as 12, or more, mg. of radium element may be packed into a needle smaller than an ordinary round surgical needle. Needles are usually made of steel, platinum or some strong noncorrosive alloy. The wall thickness of steel needles is usually $\frac{4}{10}$ mm., the length 2.7 cm. and the outside diameter 1.75 mm. While platinum is nearly 3 times as dense as steel, and a platinum needle will furnish about 3 times as much metal screening as if steel of the same thickness were used, the softness of even "hard" iridioplatinum renders this metal less useful. Speaking very generally, steel needles having a wall thickness of $\frac{1}{10}$ of a millimeter and containing 10 or 12 mg. of radium element should not be left in the tissues over eight to twelve hours. The total amount of radium element contained in the needles should not be over 50 or 60 mg. unless the physician has had the experience with the method and the cases are carefully selected.

When radium emanation is available, its use is to be recommended instead of radium sulphate on account of certain mechanical advantages and the absence of the danger of losing the radium. As homogeneity of action on all the tumor cells is the ideal to be achieved, it is preferable to use several needles of weaker strength implanted in different parts of the growth rather than one powerful needle.

3. **Flat Plates, or Plaques, on Which the Radium Salt is Spread.**—The plaques may be composed of linen, rubber or metal. Flexible applicators that may be bent and thus adapted to the convexities and concavities of the skin surface may be made of the former two materials. Linen applicators are known as "toiles." The best type of metal applicator is made of silver, the radium salt being spread uniformly over a glazed surface which forms the face of the applicator. Lead free glass must be used. Plaques of this type are known as glazed radium applicators. These have practically replaced the older varnish applicators. The glazed surface applicators may be made of any desired shape but the surface must be flat. Attention must be paid to the degree of concentration of "spread radium" as it is evident that different effects are produced by variations of this factor.

Expressed in terms of radium element, which is the common standard in this country, "full strength," "half strength" and "quarter strength" applicators contain, respectively, 5.00 mg., 2.5 mg., and 1.25 mg. of radium element to the square cm. The strength of each applicator is always approximate.

A convenient type of applicator is a square plaque 2 x 2 cm., and of "half strength," i.e., containing 10 mg. of radium element. Other plaques may be smaller or larger, round or oval, and contain less, or more, radium. Screens of any desired thickness may be placed over the face of the plaque just as when tubes are used. Lead or silver screens having

a thickness of 1/10, 5/10 and 1 mm. are convenient. Varied proportions of the beta rays may thus be filtered out in order to prevent, when thought advisable, too much action on the superficial layers of the skin. The plaques have the great advantage over the usual capillary glass tubes enclosed in silver of permitting a greater utilization of the beta rays. This is desirable in some types of angioma, epithelioma, etc. The plaques also emit a more uniform radiation on account of their plane surface. They are most useful in certain skin disorders, notably angiomata, in which the cosmetic result is important. The disadvantage of the plaques lies in their relatively large size which practically limits their use to the skin surface.

When using plaques with metal screens, it is customary to place first over the face of the plaque the desired metal screen. Over the screen 10 or 12 thicknesses of thin paper are then placed in order to absorb the secondary rays. In some cases one or more mm. of paper or other nonmetallic material may be used. The whole apparatus is then wrapped in rubber dam and applied to the lesion with adhesive tape, or a bandage.

B. APPARATUS CONTAINING RADIUM EMANATION

We have already said that both radium and radium emanation emit only alpha rays which do not escape from the tube containing them. The real source of the penetrating rays is the decay products, radium B and radium C, and especially the latter.

When radium salts are confined in a tube the only function of radium itself and its next decay product, radium emanation, is to produce radium B and radium C as fast as these latter decay. It is evident then, that if we can separate the radium emanation from the solid radium and confine it in a glass tube, radium B and C will be produced by disintegration of the emanation and will themselves constitute the source of penetrating beta and gamma rays. In other words, the capillary glass tube in which the emanation is confined may be used to radiate the tissues exactly as if it contained radium itself. Inasmuch, however, as radium emanation decays quite rapidly, falling to ½ its original amount in 3.85 days, the radiations from this source are not constant as is the case when radium itself is used.

Objection to the use of radium emanation alone as a source of therapeutic radiations has been made on the ground that the relatively rapid loss of activity impairs its value. This objection can easily be met by remembering that few treatments exceed 24 hours in duration and during this time only 16 per cent of the initial activity of the emanation is lost. For the production and collection of radium emanation for therapeutic use at least 1 gram, or more, of radium element is desirable from a practical point of view. The salt used is radium chloride which is dissolved in water to which a small quantity of hydrochloric acid has been added.

The extraction, purification, and compression into a small bulk of the radium emanation from this solution is a highly technical and complicated procedure requiring special apparatus. For the description of the process the reader is referred to a previous chapter.

The advantages of radium emanation tubes over tubes containing radium salts are numerous; among them may be mentioned the following: (1) The minute size of the emanation tubes. It is easily possible to make an emanation tube less than $\frac{1}{10}$ or even $\frac{1}{100}$ the size of a tube of similar activity containing radium sulphate. (2) The greater flexibility of the armamentarium, since tubes or applicators of any size, shape or strength may be made. (3) The obviation of danger of loss of the radium since the radium itself is not actually used in the therapeutic applications. On the other hand, for certain surface applications and especially in treating many skin diseases radium plaques are preferable to the emanation apparatus on account of their greater convenience, constant dosage and at close range their more uniform radiation.

Apparatus designed for the practical application of radium emanation consists of:

(1) Capillary glass tubes, in which the emanation is confined. These tubes vary in length from 3 to 20 mm., the outside diameter being from 0.3 to 0.6 mm. They may easily be made of any desired strength. When intended for external radiations, they may contain ordinarily from 5 to 50 mc. each. Emanation tubes of less strength may be grouped together on pads so that the effective utilization of the weakest tubes is possible. When intended for external radiations, silver tubes are slipped over the emanation tubes as soon as the latter are sealed off from the emanation machine. These silver tubes are open at both ends. They are 16 mm. long, 3 mm. in diameter and have a wall thickness of 0.5 mm. Enclosed in the silver tubes before the active deposit has formed, the emanation tubes may be conveniently handled in this manner with less danger to the operator. The emanation tubes are retained in the silver tubes by a paraffin plug at each end of the latter. The tubes are then set aside for three and one-half hours, at the end of which time the strength of each tube is measured. The silver tubes are distinguished from each other by means of a coating of enamel, of different colors or combination of colors, an ingenious method devised by Failla. A record is kept of the number of millicuries contained in each enameled tube so that its strength may be calculated from day to day.

Glass emanation tubes are sometimes used without filters. They may be laid on the surface of a growth or may be used for insertion into tumor tissue. They are often called "bare tubes" or ampoules to indicate the fact that they are used in this manner. The "bare tubes" used for insertion into tumor tissue are ordinarily about 3 mm. in length and have a diameter of about 0.3 mm. They usually contain from 0.5 to 3

mc. of emanation. They may be made by cutting up longer emanation tubes by means of a minute gas flame. As the pressure of the emanation in the tube is less than atmospheric pressure, no emanation is lost by this procedure. Failla has devised an ingenious machine by means of which a glass tube may be cut into shorter lengths with great rapidity. The method of using the bare emanation tubes by inserting them into the tumor tissue is described in a subsequent chapter. We have devised an instrument for the convenient insertion of ampoules (Fig. 36).

(2) Special steel needles, devised by Joly and Stevenson, in which the

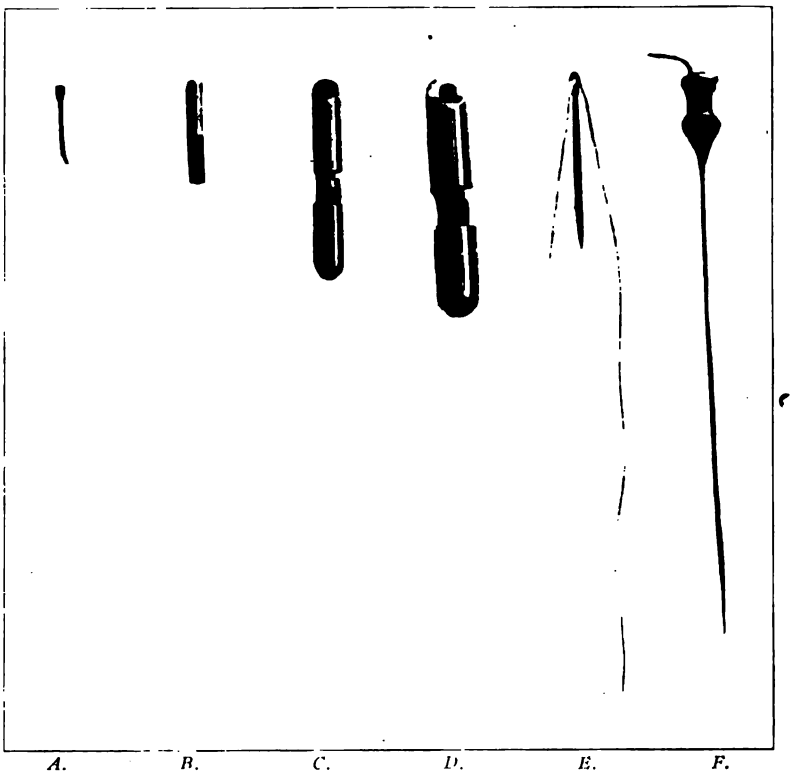


Fig. 20.—Apparatus for the application of radium emanation.

A, Capillary glass emanation tube, length 7 mm., outside diameter $\frac{5}{10}$ mm. *B*, Enameled silver tube, length 1.6 cm., wall thickness $\frac{5}{10}$ mm. to contain glass emanation tube *A*. *C*, Brass screen, length 2½ cm., wall thickness .62 mm. to contain silver tube *B*. *D*, Brass screen, length 3 cm., wall thickness 1.8 mm. to contain silver tube *B*. *E*, Hollow steel needle with screw cap, length 17 mm., wall thickness $\frac{1}{10}$ mm. to contain emanation tube *A*. Into a similar needle may be packed about 12 mg. radium sulphate, the cap being then hermetically sealed on. *F*, Hollow steel needle with plunger to contain glass emanation tube *A* after removal of plunger. The needle may then be inserted into the tumor for the required number of hours. From this needle may also be ejected by means of the plunger a similar but more minute capillary glass emanation tube which may be allowed to remain in the substance of a growth. The author's instrument for the convenient insertion of glass ampoules is shown in Fig. 36.

capillary glass emanation tubes may be placed. The steel needle, containing the emanation tube, may be inserted into the substance of tumors. These steel needles have a wall thickness of 0.3 to 0.4 mm. and a length of from 1 to 2 cm. The needle containing the glass emanation

tube is withdrawn from the tissues after the required length of time has elapsed. Instead of steel, the needles may be made of platinum or any other desired material. In estimating the time of exposure, due regard must be paid to the amount of screening power possessed by the wall of the needle. This method of using needles has been replaced in large measure by the method previously described in which bare emanation tubes are inserted and left to decay in the tumor tissue. In some cases, however, the use of metal needles is desirable.

C. APPARATUS FOR USING THE RADIOACTIVE DEPOSIT

The field of usefulness for the active deposit is relatively small at the present time. The active deposit may be utilized, however, in several ways. These are (1) the deposit may be allowed to collect on a small piece of metal such as lead foil. (2) The deposit may be collected on a wire attached to the negative pole of a battery. Radioactive wires may be utilized by insertion into the tissues. (3) A solution of active deposit may be used.

1. The Active Deposit Collected on Metal

We have already stated that when radium emanation is separated from the radium and confined in a tube, a thin coating or film of "active deposit" forms on the walls of the tube and that the tube itself may then be used as a source of radiation, the function of the emanation being simply to keep up the supply of "active deposit." We may even go a step further. Once the active deposit has settled on the walls of the tube, the emanation itself may be taken away and the active deposit alone may be used as a source of radiations. Under these circumstances, however, the tube is short lived as the emanation is lacking to replenish the active deposit as fast as it decays.

If a small piece of metal such as lead foil is enclosed for three to four hours in a container with the emanation, the metal becomes coated with "active deposit" and may be removed from the container and used alone as a source of radiations. Radioactive lead foil has been used principally for the treatment of vernal conjunctivitis.

2. Radioactive Wires

By a suitable arrangement, a platinum wire may be attached to the negative pole of a battery and inserted into a glass bulb into which the emanation may be introduced. The radium A that is formed from the emanation has a positive charge. It goes, therefore, as Rutherford first observed, to the negative electrode and is deposited there. There is thus formed "radioactive deposit" on the wire, the maximum amount being obtained after about three hours. The radiation from the wire consists

of alpha, beta and gamma rays. Just as in the case of the piece of metal enclosed in the emanation chamber and previously referred to, the "activity" of the wire decays rapidly.

As shown by Lyster and Russ, an "active wire" may be of value when introduced directly into the tissues. Under these conditions, the radiations do not suffer any loss by absorption in the apparatus such as happens when the ordinary radium emanation container is used. As will be seen by referring to the following table, however, the radioactivity of the active deposit falls to less than half value in one hour. The short life of the active deposit thus curtails its usefulness.

TABLE XIII

(After Colwell and Russ.)

RATE OF DECAY OF RADIOACTIVE DEPOSIT			
ALPHA RAYS		GAMMA RAYS	
TIME	ACTIVITY	TIME	ACTIVITY
0 minutes	100	0 minutes	100
10 "	53	10 "	96.6
20 "	46	20 "	88.4
30 "	40	30 "	-
40 "	35	40 "	66.9
50 "	30	50 "	-
60 "	26	60 "	38.5
1 hr. 30 min.	14	1 hr. 30 min.	25.3
2 hr. 00 "	7.2	2 hr. 00 "	12.9
3 hr. 00 "	1.8	3 hr. 00 "	3.1

3. Solution of Active Deposit

The active deposit may be dissolved in water or allowed to collect in a closed chamber on some soluble substance such as common salt which may then be dissolved. The solution may then be injected, subcutaneously or intravenously. The method of preparing a solution of active deposit has been described in a previous chapter.

CHAPTER XIII

DOSAGE

A scientific and perfected method of dosage in radium therapy would demand that the rays coming from each apparatus be carefully measured and directed in accordance with our knowledge of the radiation necessary to destroy each normal and diseased cell complex. These ideal conditions for treatment cannot be completely fulfilled.

In the first place we are dealing with the living organism and even if the rays could be measured for each applicator and directed properly the intensity of radiation necessary to produce certain results will vary to some extent with the individual tissue or tumor that is treated. Within certain limits, however, the proper measuring of the dose of rays is of the highest importance and is the foundation of a scientific therapy. The number of possible arrangements of apparatus containing radium is so great that we must limit ourselves to a discussion of a few types of applicators that are adaptable to a number of conditions. We shall give, however, the results of certain mathematical calculations that are of value in enabling us to estimate the intensity of the radiations from different types of applicators at different distances.

In considering the subject of dosage we must distinguish between (a) surface radiations, i.e., radiations that are delivered by placing the apparatus at various distances from the surface of the skin or mucous membranes, and (b) intratumoral radiations, i.e., radiations that are derived from the actual introduction of the radioactive material into the substance of tumors.

SURFACE RADIATIONS

Neglecting for the moment the radiosensitiveness of the tissues, the therapeutic effect of radiations depends upon their quality, their intensity and the duration of the exposure. The quality of the radiations depends upon the filtration. The intensity of the radiations at a given point depends upon:

1. The quantity of radioactive material.
2. The filtration.
3. The shape of the source, i.e., the method of distribution of the radium on the apparatus.
4. The distance from the source.
5. Absorption in the apparatus and in the tissues.
6. The secondary radiations in the tissues.

A marked variation of any one of these factors naturally alters

the effect of the radiation. We may now consider the effect of each factor.

(1) The Quantity of Radium or Radium Emanation in the Apparatus

It is evident that, other things being equal, the larger the quantity of radioactive material the more intense is the radiation. Speaking very generally the quantity of radium used naturally depends upon the purpose of the radiation, i.e., whether the lesion requires a mild or intensive dosage and whether superficial or deep effects are desired. The quantity used varies therefore from a few milligrams which may be suitable for superficial cosmetic disorders of the skin to one gram or more which may be necessary for influencing deeply seated or extensive malignant tumors. It has already been stated that experience has shown that tubes and plaques containing from 5 to 50 milligrams of radium element or tubes containing the same number of millicuries of emanation are the most convenient and useful. Almost any combination of apparatus to augment the amount of radium for a single case may be employed. Combinations of apparatus to increase the quantity of radium and therefore the dose are made in accordance with certain mathematical calculations and as the result of experience in dealing with special kinds of lesions.

It must be especially emphasized that while there is probably an optimum dose and method of treatment, equally good results may be achieved in many cases by very different methods. The various factors mentioned above that enter into the effect of the radiation may all differ with different operators and yet the final result may be equally good. Wickham long ago insisted upon the fact that we cannot be too dogmatic, or use a too "cut and dried" method in matters pertaining to radium therapy. In children, the dose should not be more than one-half and in the case of very young children not over one-fourth of the normal dose for adults.

(2) The Filtration

We have discussed in a previous chapter the use of metallic and nonmetallic screens to filter out or absorb types of radiations that are sometimes undesirable before they reach the skin. In routine practice, the metal screens over the radium vary in thickness from 0.1 mm. to 2 mm. while the nonmetallic material used, in addition, may vary from 1 mm. to 1 or more cm.

In general, when superficial effects are desired, little or no metal screening may be used from a theoretical point of view, as the first centimeter of tissue absorbs practically all the beta rays. Although under these circumstances, both beta and gamma rays take effect, the quantity of beta rays greatly exceeds that of gamma rays while their absorption takes place readily; therefore their action greatly preponderates in short unscreened exposures. Great care must be observed, however, in using a preponderance of beta rays on the skin, as painful burns may be easily

is seldom wise to use varnish or glazed apparatus or bare
es without a certain amount of metal screening unless the
had experience with the method.

effects are desired, all of the beta rays and some of the
rays should be absorbed by a screen of brass 2 mm. thick
ivalent of another metal. Only the hard gamma rays are
in penetrating the screens and affecting the tissues.

The n for the use of thick metal screens, in the treatment of deeply s ated tissues is thus very evident. If an unscreened radium preparation is use l. the greater part of the radiation, consisting of beta rays, will be absorbed nc of tissue. As a result of this absorption, the ficial layers may ve an amount of rays sufficient to destroy them , e the deeper tiss will receive relatively little radiation. On the other hand if screening of sufficient thickness, such as may be furnished by two millimeters of brass, is used, the superficial and deep layers of tissue may receive appr timately the same amount of radiation. As many types of tumor cell are more sensitive to the rays than normal cells, the purpose of the r iation, i.e., the destruction of tumor cells and the preservation of the nc nal cells may be accomplished.

TABLE XIV

This table shows the ionizing effect due to beta and gamma rays in air. At the same distance (1 cm.) if absorption is not considered, the ionization due to beta rays may be assumed, according to Eve's experiments, to be thirty-four times that due to gamma rays. We may also accept Eve's values for the coefficients of absorption, i.e., for beta rays .012; for gamma rays, a value so small as to be negligible.

The table illustrates the effect of a filter of sufficient thickness to absorb all but gamma rays in causing a diminution of the total intensity.

DISTANCE IN CENTIMETERS	EFFECT		
	BETA RAY	GAMMA RAY	TOTAL
1	3360	100	3460
2	830	25	855
3	365	11	376
4	203	7	210
5	128	4	132
6	88	3	91
7	64	2	66
8	48	2	50
9	38	1	39
10	30	1	31

Let us now consider the effect of

(3) The Shape of the Source and

(4) The Distance of the Source from the Surface

From a theoretic point of view, the radium preparation may be distributed on an applicator of almost any desired shape or size. Thus,

radium emanation may be concentrated at one or more points or lines; radium salts may have a linear distribution, as in the case of tubes, or they may be spread uniformly over plates of various shapes and sizes. Practically, we limit ourselves to the use of tubes (i.e., a linear distribution) containing either radium emanation or salts, and to the use of round, square or rectangular plaques of various sizes containing radium salts.

It may be shown by mathematical calculation that the difference between the effect due to a linear distribution (i.e., a tube several millimeters long) and that due to a point is not more than a fraction of 1 per cent at a distance of several centimeters. The orientation of the tube at these distances is also unimportant.

We are concerned chiefly, therefore, with the effect of tubes and of plaques which may be used singly or in combination. We may now consider the variation in intensity of the radiations at different distances when the source is

(a) A single point, or a line several mm. long, i.e., a single tube.

(b) A number of points or lines, i.e., several tubes.

(c) A plane surface such as may be formed by one or more plaques or by laying a number of tubes side by side.

(a) **Single Tubes**

Considering each tube as a point source, the variation of the concentration of the rays with distance is in accordance with the law of inverse squares, i.e., the intensity of the rays varies inversely as the square of the distance from the source, any effects of absorption being, for the moment, neglected.

Let us assume that we have a source of gamma rays (filtered to absorb beta rays) so small that it may be considered as a point. Let this source be situated in a medium such as air which does not appreciably absorb the gamma rays. We may consider the point as a source of radiant energy which is emitted equally in all directions.

If we assume that a sphere of unit radius is drawn about the point source as a center, all of the radiation will go through the surface of this sphere. As there is nothing to distinguish one portion of the spherical surface from another, we can assume that the energy passing through a unit area of such a surface is a measure of the intensity at that distance from the point.

Now suppose the unit area is moved out to a distance of two centimeters. It is now part of the surface of a sphere of area $4\pi(2)^2$ instead of $4\pi(1),^2$ i.e., of a surface with four times the area of the first sphere. The energy that passed through the spherical surface of radius 1, must now pass through the spherical surface of radius 2, but it will be spread over four times the area over which it was previously distributed. Hence

the amount of energy passing through the unit area, which we have taken as a measure of the intensity, is just one-fourth, at a distance of 2 cm. from the source, of the intensity at a distance of 1 cm. from the source. Similarly, at a distance of 3 cm., it is $\frac{1}{9}$ of the intensity at 1 cm.; at 4 cm., $\frac{1}{16}$ and so on. The intensity due to a point source varies inversely therefore as the square of the distance. Consequently, if the source is a single tube, a variation in the distance of the source from the surface of even a few millimeters is sufficient to cause an appreciable difference in effect. From the standpoint of homogeneity of radiation, it is frequently desirable to place the radium tube at a distance of a few millimeters from the surface. For example, neglecting absorption for the moment, a layer of tissue, 5 mm. thick, placed 1 mm. distant from the radium tube emitting only gamma rays would receive on the far side, which is 6 mm. distant, $\frac{1}{36}$, i.e., $(\frac{1}{6^2})$ of the dose received on the near side, which is only 1 mm. distant. If the same layer of tissue were placed 5 mm. away from the radium, it would receive on the far side, which is 10 mm. distant, only $\frac{1}{4}$ (i.e. $5^2/10^2$) of the dose received on the near side, which is 5 mm. distant. It is evident, therefore, that by placing the radium tube at a certain distance from the skin, the different layers of tissue will receive more uniform radiation. In actual practice, this principle, whenever practicable, may be taken advantage of and several millimeters to one or more centimeters of gauze, rubber or wood may be interposed between the metallic screen over the radium tube and the skin, in order to give the desired distance. This material thus serves the double purpose of absorbing the secondary rays from the apparatus and also of retaining the radium tube at the proper distance. In order to compensate for the falling off in intensity of the rays due to the increased distance of the radium, proper increase in either the quantity of radium or the duration of the exposure or both of these factors must be made.

When the radium tube is introduced into a small cavity such as the interior of the uterus, it is, of course, seldom possible to keep the tube more than a few millimeters distant from the tissues. Under these circumstances, the tissue nearest the tube receives a dose that is frequently excessive but in this particular situation no ill effects are ordinarily observed. On the skin, however, an unnecessary and undesirable reaction would be produced if the radium tube is in too close apposition to it. As has been stated before, when very superficial effects are desired, the radium tube may be placed in relatively close contact with the tissue, but caution must be exercised under these circumstances, however, not to prolong the duration of the exposure beyond the proper limits, as a painful reaction may be easily produced. As we have seen, when deeper effects are desired, the radium tube may advantageously be placed at least a few millimeters away from the lesion or several tubes may be used simultaneously at a distance of several millimeters or centimeters, so as to

cover the area occupied by the lesion. The latter arrangement, which is ordinarily the better one, will be considered in a subsequent section.

It may be found by experiment that fifty millicuries, contained in a point or minute tube, screened to absorb all but gamma rays will produce, at a distance of 1 cm., an erythema of the skin in twelve hours, i.e., 600 mc. centimeter hours. (50 × 12.)

Let us assume the permissible skin dose to be 600 mc. centimeter hours. We can now find, at least theoretically, the smallest distance from the skin at which, for example, a fifty millicurie tube can be left for an hour. This is easily done as follows, if we consider the tube as a point source:

The intensity at any point at a distance r from the source is $\frac{50.}{r^2}$ We wish this intensity, when multiplied by the time in hours (*1* in this case) to be equal to 600.

$$\text{Hence } \frac{50}{r^2} = 600 \qquad r^2 = 1/12 \qquad r = 1/6\sqrt{3} = .29 \text{ cm.}$$

or approximately 3 mm. Actually the tube can be placed closer than this, since a tube is not a true point source. The intensity at .29 cm. away is not 600 but is given by

$$\frac{d_1}{f}\left[\tan^{-1}\frac{a+l/2}{f} - \tan^{-1}\frac{a-l/2}{f}\right] = \frac{2.M}{lf}\tan^{-1}\frac{l}{2f}$$

a being equal to zero in this case.

where M is number of millicuries in the tube, l its length, f the distance away. Take $M = 50$, $l = .7$, $f = .29$. We get for the intensity at .29 cm.,

$$\frac{100}{.7(.29)}\tan^{-1}\frac{.7}{.58}, \text{ or } 433.$$

This is about two-thirds of that permissible. Hence to approximate to the possible distance, try $.29\sqrt{2/3} = .236$ cm. The intensity at that distance is

$$\frac{100}{.7\ (.236)}\tan^{-1}\frac{.7}{.472} = 592.$$

Hence .235 cm. is as near to the skin as one may leave a 50 millicurie tube for an hour. If we accept as approximate the rule that for the same value of distance times the time, with the same intensity, the effect is the same, this will also be the minimum permissible time to leave a 25 mc. tube for two hours, a 100 mc. tube for one-half hour, etc., since $25 \times 2 = 100 \times 1/2$. The above rule holds, however, only within certain limits as we shall show later on.

(b) Several Tubes

Let us now consider two 50 mc. point sources. Let us try to give three points on the skin the same amount of radiation. Let us take one

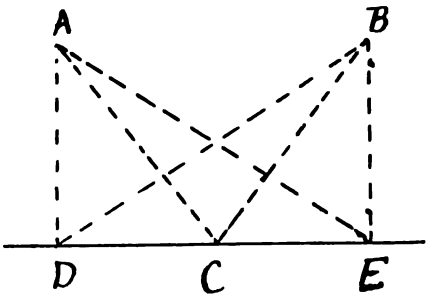


Fig. 21.—Diagram showing two radium tubes affecting three different points on skin.

point directly below each tube, and the third point halfway between them. Let A and B be the two tubes, D, E, and C the points on the skin. (Fig. 21.) The intensities at D and E will, from symmetry, be the same. Let us assume the intensity at D and also at E to be 600. Then the intensity at C due to A is $\frac{50}{AC^2}$. That at C due to B is $\frac{50}{BC^2}$. Now $AC = BC$ if the midpoint of DE is C. Hence the total intensity at C is $\frac{2 \times 50}{AC^2} = \frac{100}{AC^2}$.

Let $\overline{AD} = Y$. $\overline{DE} = X$

Then $\overline{AC}^2 = \overline{AD}^2 \times \overline{DC}^2 = Y^2 + \frac{X^2}{4}$

" $\frac{100}{Y^2 + \frac{X^2}{4}} = 600$ or $Y^2 + \frac{X^2}{4} = \frac{1}{6}$

The intensity at D due to A is $\frac{50}{AD^2}$ or $\frac{50}{y^2}$. The intensity at D due to B is $\frac{50}{BD^2} = \frac{50}{BE^2 + DE^2} = \frac{50}{Y^2 + X^2}$. The sum of these two intensities is to be 600.

$$\frac{50}{Y^2} + \frac{50}{Y^2 + X^2} = 600 \text{ or } \frac{1}{Y^2} + \frac{1}{Y^2 + X^2} = 12$$

We have therefore two equations.

$$Y^2 + \frac{X^2}{4} = 1/6$$

$$\frac{1}{Y^2} + \frac{1}{Y^2 + X^2} = 12$$

We can solve these for X^2 and Y^2 and hence get the desired distances AD and DE. We find for AD, the distance from the skin, .333 cm. and for AB, the distance apart of the point sources, .471 cm.

On the other hand, if we use tubes instead of point sources, we find that

with the distances as given, the intensity at D and E amounts to 482. Hence we must approximate as before by decreasing the distances in the ratio $\sqrt{4/5}$. By several such approximations (we need here to correct the ratio $\frac{\sqrt{AD}}{\sqrt{AB}}$ as well as $\sqrt{AD}$ and $\sqrt{AB}$ together) we arrive at the values. Distance from skin = .289 cm.; distance apart = .440 cm.

The same procedure can be followed for points and tubes at the corners of an equilateral triangle and also at the corners of a square. The results are given in Table XV.

TABLE XV

THEORETIC MINIMUM PERMISSIBLE DISTANCE FROM SKIN FOR 50 MC. FOR ONE HOUR

	POINT SOURCES		TUBES 7 MM. LONG	
	DISTANCE FROM THE SKIN	DISTANCE APART	DISTANCE FROM SKIN	DISTANCE APART
Single tube	.289 cm.	.0	.235 cm.	.0
Two tubes	.333 "	.471 cm.	.289 "	.440 cm.
Three "	.353 "	.612 "	.312 "	.307 "
Four "	.375 "	.619 "	.332 "	.595 "

If we wish to change the amount of radium, we must change either the time or the distance. If the distance be kept constant, the time should be changed in such a way that the numerical value of the product obtained by multiplying the number of millicuries by the time in hours is kept the same. In general two arrangements of point sources (or of tubes at a distance of more than a few centimeters) are similar in effect when we have the same value for $\frac{(\text{Amount of radiating substance})\ (\text{Time})}{(\text{Distance})^2}$ for each distance, i.e., for the distance apart of the tubes and also the distances from the skin. Thus if we increase the time from one hour to six, we must, for point sources, increase the distance each in the ratio $\sqrt{6}$ etc.

TABLE XVI

THEORETIC MINIMUM PERMISSIBLE DISTANCE FROM SKIN FOR 50 MC. FOR SIX HOURS

Assuming the maximum permissible dose as 50 mc. at 1 cm. for 12 hours, the minimum permissible distances for 50 mc. for 6 hours will be

	POINT SOURCES		TUBES	
	DISTANCE FROM SKIN	DISTANCE APART	DISTANCE FROM SKIN	DISTANCE APART
Single source	7.10 mm.		6.79 mm.	
Two sources	8.16 mm.	11.53 mm.	7.92 "	11.56 mm.
Three "	8.64 "	14.99 "	8.47 "	14.96 "
Four "	9.18 "	15.18 "	9.01 "	15.19 "

For tube sources, this method gives only approximate results, due to the departure from the inverse square law. It must be especially empha-

sized, however, that biologically the method of calculation outlined above does not hold true for all intensities and times. The actual biologic effects can only be determined by experience. For small variations of intensity and time the above method is approximately correct. The effect due to a large intensity for a short time is not the same, however, as that due to a small intensity for the correspondingly longer time. We shall refer to this point again in our discussion of the duration of the exposure.

From the foregoing, it may be stated that, in general, two equal sources or tubes may be placed with their centers approximately twice as far apart as their distance from the skin. This arrangement provides an approximately uniform field of radiation at the skin surface. The foregoing rule does not hold, however, in the case of large extended sources as we shall show later on. Three equal sources or tubes may be placed at the corners of an equilateral triangle.

Four equal sources or tubes may be arranged at the corners of a square, if we wish to make the intensity beneath the center of the square equal to that under each of the four corners.

In the case of the equilateral triangle and the square (3 tubes and 4 tubes respectively) the same general rule holds as in the case of two tubes, i.e., the sides of the triangle and the sides of the square may be approximately twice as long as the distance of the tubes from the skin.

(c) Plaques.—Tubes Laid Side by Side

It is evident that as the number of tubes is increased the effect approaches very closely to that produced by a plaque, i.e., by a uniform distribution of the radioactive material on a plane surface. At a distance of a few millimeters, the plaque source has a slight advantage over the multiple tube source in that the former produces an approximately uniform field of radiation. This uniformity of effect is of considerable importance in the treatment of cosmetic skin disorders, such as angiomata. At a distance of several centimeters, both types of apparatus have an almost identical effect.

We may now give some illustrations of the relative effects of a few different types of applicators. For convenience, the gamma ray intensity derived from a point source containing one mg. of radium element at a distance of one centimeter, is taken as the unit in all of the following calculations.

In calculating Table XVII each tube was considered as a point. The calculation was also made for 25 tubes considering each tube as a line; the result was 9.941, a difference from 9.946 of $\frac{1}{20}$ per cent.

The intensity decreases as the number of tubes increases, approaching the value for a uniform distribution which may be estimated from the above table as approximately 9.8, i.e., a difference of only about 2 per

TABLE XVII

EFFECT OF DIFFERENT NUMBERS OF TUBES CONTAINING A TOTAL QUANTITY OF 500 MG. DISTRIBUTED OVER A PLANE SURFACE 10 X 10 CM. DISTANCE FROM PLANE OF TUBES TO POINT ON AXIS IS ASSUMED TO BE 6 CM. ABSORPTION IN THE APPARATUS IS NOT CONSIDERED

NUMBER OF TUBES	GAMMA RAY INTENSITY AT A POINT ON THE AXIS, 6 CM. FROM THE PLANE OF THE TUBES
1	13.88
4	10.31
16	9.99
25	9.95
100	9.89

cent from the value for twenty-five tubes. The advantage in increasing the number of tubes (i.e., sources) beyond 15 is not immediately apparent for a distance of 6 or more cm. from the skin.

Tables XVIII and XIX illustrate the difference in effect of a plaque and a point source respectively at various distances. As we have already

TABLE XVIII

INTENSITY OF GAMMA RADIATION DUE TO A CIRCULAR PLATE 4 CM. IN DIAMETER AND A POINT SOURCE, RESPECTIVELY. EACH TYPE OF SOURCE IS ASSUMED TO CONTAIN 50 MG. OF RADIUM ELEMENT. THE INTENSITY IS CALCULATED AT A POINT ON THE AXIS OF THE PLATE, I.E., ON A LINE PERPENDICULAR TO ITS CENTER. ABSORPTION IN THE APPARATUS IS NOT CONSIDERED.

DISTANCE IN CM. OF THE SOURCE FROM THE SURFACE	CIRCULAR PLATE 4 CM. IN DIAMETER, CONTAINING 50 MG. RADIUM ELEMENT. (ABOUT 4 MG. PER SQ. CM.)	POINT SOURCE CONTAINING 50 MG. RADIUM ELEMENT
.1 cm.	74.8	5000
.2 "	57.7	1250
.3 "	47.7	555
.4 "	40.7	313
.5 "	35.4	200
.6 "	31.1	139
.7 "	27.7	102
.8 "	25.4	78
.9 "	22.3	62
1.0 "	20.1	50
1.2 "	16.6	34.7
1.5 "	12.8	22.2
1.6 "	11.8	19.6
2.0 "	8.67	12.5
2.5 "	6.17	8.00
4.0 "	2.79	3.13
6.0 "	1.32	1.39
8.0 "	.76	.78
10.0 "	.49	.50

shown, the plaque source and the multiple tube source are practically equivalent, at least at a distance of several centimeters, in the production of a homogeneous field of radiation at the surface.

TABLE XIX

INTENSITY OF GAMMA RADIATION DUE TO A CIRCULAR PLATE 10 CM. IN DIAMETER AND A POINT SOURCE, RESPECTIVELY. EACH TYPE OF SOURCE CONTAINS 500 MG. RADIUM ELEMENT

THE INTENSITY IS CALCULATED AT A POINT ON THE AXIS OF THE PLATE. ABSORPTION IN THE APPARATUS IS NOT CONSIDERED

DISTANCE IN CM. OF THE SOURCE FROM THE SURFACE	CIRCULAR PLATE 10 CM. IN DIAMETER CONTAINING 500 MG. RADIUM ELEMENT (ABOUT 6.36 MG. PER SQ. CM.)	POINT SOURCE CONTAINING 500 MG. RADIUM ELEMENT
1 cm.	65.2	500
2 "	39.6	125
3 "	26.6	55.6
4 "	18.8	31.3
5 "	13.9	20
7 "	8.24	10.2
10 "	4.46	5.0
15 "	2.11	2.22
20 "	1.21	1.25
25 "	.784	.800

Tables XVIII and XIX show that so far as the axis and direct radiation are concerned, there is little difference in the effect of the two types of sources at a distance of more than 7 cm. Closer than this the intensity due to the point source becomes much the greater. Hence if the skin is closer than 6 cm. an extended source (i.e., either plaques or a number of tubes) may be used to greater advantage than a point source for deep treatments. If the skin is nearer than 1 cm., as in superficial treatments, the plaque source is particularly advantageous in comparison with a point source.

The advantage of the extended or distributed source lies in the fact that it can be put nearer to the skin than the point source, and, while producing the same effect on the skin itself, it gives a greater effect at a point below the surface. Thus, if 20 were the limiting dose for the skin in the above example, the point source must be at least 5 cm. away, while the extended source can be put within less than 4 cm. of the skin. In the latter case, the intensity 5 cm. below the skin surface would be 5 for the point, 5.5 for the distributed material, i.e., 10 per cent higher for the latter. For a distance of 3 cm. below the skin surface, the advantage is less than 4 per cent; for 10 cm., about 10 per cent. There are, in addition, certain technical reasons on account of which a distributed or widely extended source is more convenient of application than a point source. Thus it is more practical to arrange on an applicator, that has,

e.g., an area of 100 square cm., 10 tubes or plaques each containing 50 mg., than a single powerful tube, containing 500 mg.

It is frequently of interest to know the theoretic variation of intensity for plaques of different sizes.

In general, for a surface distribution, if one reduces every dimension in the same ratio, keeping the surface density (amount per sq. cm.) constant, the intensity at any given point can be found for the new distribution from the intensity of the corresponding point, respectively, in the old distribution by multiplying the given distances by the "ratio of reduction." Thus, for a circular disk of radius 5 cm., using 500 mg., the field at a distance of 1 cm. is the same as for a circular disk of radius 2 cm. $(5 \times .4)$ using 80 mg. $(500 \times (.4)^2)$ at a distance of 4 mm. $(1 \times .4)$; that for a distance of 2 cm. is the same as for the second case at 8 mm. and so on. While from a physical standpoint the intensity may be calculated as outlined above, the biologic effect may not be the same for plaques of different sizes.

Table XX shows the variation in gamma ray intensity at different distances due to a square plate, on which 12 tubes are symmetrically arranged, and to a point source, respectively.

From a practical point of view, the more superficial the situation of the lesion, other things being equal, the closer to the skin the radium may be placed, and vice versa, the deeper the situation of the lesion, the farther away from the surface of the skin the radium should be placed.

In employing superficial radiations, the overlying skin or mucous membrane frequently but not necessarily becomes markedly inflamed or even destroyed. Inflammatory reaction should be avoided, as a rule, when possible. When employing deep radiations, it is usually desired to preserve the overlying skin or mucous membrane. Hence, only a slight amount of surface

TABLE XX

GAMMA RAY INTENSITIES DUE TO A SINGLE 6 X 6 CM. PLATE, CONTAINING 200 MG. IN 12 TUBES. ABSORPTION IN THE APPARATUS IS NOT CONSIDERED.

DISTANCE FROM AXIS	DISTANCE FROM PLATE=6 CM.		DISTANCE FROM PLATE=10 CM.	
	12 TUBES	POINT SOURCE	12 TUBES	POINT SOURCE
0 cm.	4.845	5.556	1.898	2.000
2 "	4.503	5.000	1.833	1.923
4 "	3.670	3.846	1.665	1.724
5 "	3.202	3.279	1.557	1.600
6 "	2.775	2.778	1.441	1.471
8 "	2.022	2.000	1.208	1.220
10 "	1.493	1.471	.998	1.000
12 "	1.128	1.111	.821	.820
14 "	.875	.862	.679	.676
16 "	.693	.685	.566	.562
18 "	.562	.556	.475	.472
20 "	.463	.459	.403	.400

TABLE XXI

GAMMA RAY INTENSITIES DUE TO TWO SUCH PLATES, OR POINTS, IDENTICAL WITH THOSE IN THE PREVIOUS TABLE. DISTANCE FROM SOURCE TO SURFACE=6 CM.

The term "center line" is used in considering the effect of two applicators arranged so that the planes containing the tubes are at the same distance from the surface but separated by an interval of space. The center line is the line perpendicular to the plane of the tubes and passing through the midpoint of the line between the centers of the surfaces of the applicators on which the tubes are arranged.

Absorption in the apparatus is not considered.

DISTANCE FROM CENTER LINE	DISTANCE APART OF PLATES = 0 CM.		DISTANCE APART OF PLATES = 4 CM.		DISTANCE APART OF PLATES = 8 CM.	
	PLATES	POINTS	PLATES	POINTS	PLATES	POINTS
1 cm.	8.173	8.846	6.445	6.624	4.797	4.778
3 "	7.620	8.334	6.525	7.000	5.163	5.317
5 "	6.525	7.000	6.338	7.027	5.631	6.111
7 "	5.163	5.317	5.631	6.111	5.720	6.418
9 "	3.903	3.889	4.545	4.708	5.196	5.685
11 "	2.897	2.862	3.468	3.463	4.232	4.402
13 "	2.186	2.156	2.584	2.556	3.238	3.237
15 "	1.690	1.667	1.956	1.950		
17 "	1.338	1.321				

TABLE XXII

GAMMA RAY INTENSITIES DUE TO TWO 6 x 6 CM. PLATES EACH CONTAINING 200 MG. IN 12 TUBES. ABSORPTION IN THE APPARATUS IS NOT CONSIDERED. DISTANCE FROM SOURCE TO SURFACE=6 CM.

DISTANCE FROM CENTER LINE	DISTANCE APART OF PLATES = 2 CM..		DISTANCE APART OF PLATES = 6 CM.		DISTANCE APART OF PLATES = 10 CM.	
	PLATES	POINTS	PLATES	POINTS	PLATES	POINTS
0 cm.	7.340	7.692	5.550	5.556	4.044	4.000
2 "	7.278	7.778	5.692	5.846	4.268	4.249
4 "	6.867	7.556	5.996	6.471	4.798	4.957
6 "	5.996	6.471	5.973	6.667	5.378	5.862
8 "	4.798	4.951	5.378	5.862	5.538	5.241
10 "	3.650	3.640	4.363	4.531	5.065	5.556
12 "	2.715	2.685	3.337	3.334	4.133	4.305
14 "	2.055	2.027	2.485	2.459		
16 "	1.591	1.570				

inflammation is ordinarily produced and in most cases it may be avoided altogether.

For certain of the most superficial effects, the radium may be placed practically in apposition with the skin or mucous membranes, especially, as we have shown, when the source of the radiations is a plane surface. For somewhat deeper effects the distance of the radium from the surface may be from 2 mm. to 1 cm.; in other cases requiring still deeper effects, from 1 to 6 cm.; for the deepest effects, from 6 to 10 or more cm. As the distance

of the source from the surface increases, the quantity of radium necessary for certain effects must be increased. While the diminution of intensity due to distance and absorption may be partly compensated for by increasing the duration of the exposure, massive deep effects cannot be pro-

TABLE XXIII.

METHODS OF CALCULATING ABSORPTION IN THE APPARATUS

Absorption coefficient = .05.

By one method, i. e., treating the absorption of the radiation from each point separately, one gets for the intensity due to 500 mg. in 25 tubes, at a point on the axis 6 cm., distant from the plane of the tubes, 6.32. By a second method, i. e., using the average distance, 6.28.

Sample calculation.

NO. TUBES	EFFECT DUE TO EACH		TOTAL EFFECT
	FIRST METHOD		
1	$.555\ e^{-(.1+.3)}$	$=.372$	.372
2	$.500\ e^{-(.1+\sqrt{\frac{1}{10}})}$	.330	.660
2	$.385\ e^{-(.1+\sqrt{\frac{13}{10}})}$	.243	.486
2	$.500\ e^{-(.1+\sqrt{\frac{1}{10}})}$	.330	.660
4	$.454\ e^{-(.1+\sqrt{\frac{11}{10}})}$	.295	1.180
4	$.357\ e^{-(.1+\sqrt{\frac{14}{10}})}$	.222	.888
2	$.384\ e^{-(.1+\sqrt{\frac{13}{10}})}$	.242	.484
4	$.357\ e^{-(.1+\sqrt{\frac{14}{10}})}$	.222	.888
4	$.294\ e^{-(.1+\sqrt{\frac{17}{10}})}$	.176	.704
			6.322
	SECOND METHOD		
	d	d	nd
1	6	6	6
4	$2\sqrt{10}$	6.3246	25.298
4	$2\sqrt{13}$	7.2112	28.845
4	$2\sqrt{11}$	6.6332	26.553
8	$2\sqrt{14}$	7.4834	59.868
4	$2\sqrt{17}$	8.2462	32.985
			25)179.528
			20)7.1812
			.35906
			.1
	$9.941e^{-.45906}=6.281$		.45906

The difference between the results of the two above methods is 2/3 per cent. Ordinarily it would be much less as in these calculations a small distance has been used.

duced without using relatively large quantities of radium. Practical experience has shown that in most cases demanding deep effects a minimum of 500 mg. is required, while in other cases not less than 1000 to 2000 mg. are necessary.

In such cases, the minimum amount of metal screening is 2 mm. of brass or its equivalent of another metal, and the distance of the radium from the surface should not be less than 10 cm.

5. Absorption

(a) **Absorption in the Apparatus.**—Let us now consider the effect of absorption in the apparatus in decreasing the intensity of the gamma radiations. For convenience, the gamma ray absorption in the apparatus has been calculated in Tables XXIII and XXIV for a medium of about the density of wood, which has an absorption coefficient of approximately .05. There are two possible ways of calculating the effect of absorption on the radiation due to a number of tubes, as shown in Table XXIII. By the first method, the absorption is calculated for each tube separately, and the resulting corrected values of intensity are added together. By the second method, the average of the thicknesses of absorbing material between the radium and the point affected is found first, and the sum of all the uncorrected values is corrected by the amount of absorption which would occur if this average distance held for all; this second method is only an approximate one, of course. In either case, whether the correction is made for each tube separately, or, using the average distance for all the tubes at once, we multiply the uncorrected value by the exponential $e^{-\mu d}$, where μ is the coefficient of absorption, d the thickness of absorbing material in question. As we have said before, μ is taken as $\frac{1}{20} = .05$ in Tables XXIII and XXIV. The absorption factor due to filtration is taken as $e^{-.1}$.

TABLE XXIV

GAMMA RAY INTENSITY DUE TO A CIRCULAR PLATE 10 CM. IN DIAMETER, CONTAINING 500 MILLIGRAMS RADIUM ELEMENT AT A POINT ON ITS AXIS, CONSIDERING ABSORPTION

This is compared with the intensity due to a point source containing the same quantity of radium.

DISTANCE OF THE SOURCE FROM THE SURFACE	INTENSITY DUE TO PLATE SOURCE	INTENSITY DUE TO POINT SOURCE
1 cm.	57.6	475.6
2 "	33.4	113.1
3 "	21.5	48.4
4 "	14.6	25.6
5 "	10.3	15.6
7 "	5.6	7.2
10 "	2.6	3.0
15 "	.99	1.05
20 "	.44	.46
25 "	.22	.23

The conclusions to be drawn from Table XXIV are (1) that absorption in the apparatus cuts down the intensity due to a distributed source more than it does that due to a point source; this is, of course, self-evident in any case, since the distributed source is under the conditions taken (point source taken at center of disk, and effect on axis considered) on the average farther away than the point source. Thus the effect on the axis at a distance of 10 cm. differs by 11 per cent without considering absorption, 13 per cent if absorption is considered, the advantage being with the point source in each case. (2) That if 20 still be the maximum skin dose possible, the point source can now be put about 4.5 cm. from the skin, the extended source 3.2 cm. (previously 5 and 3.8) i.e., the superiority of the latter in this respect is increased. The intensity 5 cm. below the skin surface for the same skin dose of 20 is now 15 per cent greater for the plaque source than for the point source and about the same (15 per cent) at a point 10 cm. below the skin surface.

TABLE XXV

GAMMA RAY INTENSITY DUE TO SINGLE 6 x 6 CM. PLATE CONTAINING 200 MG., RADIUM ELEMENT IN 12 TUBES, EVENLY DISTRIBUTED ON THE SURFACE. ABSORPTION IN THE APPARATUS IS CALCULATED BY THE APPROXIMATE METHOD

	PLATE SOURCE		POINT SOURCE		PLATE SOURCE		POINT SOURCE
	EXACT METHOD	APPROXIMATE METHOD			EXACT METHOD	APPROXIMATE METHOD	
6 CM. AWAY AND ON AXIS	3.180	3.178	3.724	10 CM. AWAY AND ON AXIS	1.028	1.028	1.097
2 cm. from axis	2.914	2.912	3.298	2 cm. from axis	.985	.983	1.045
4 " " "	2.295	2.276	2.426	4 " " "	.872	.870	.910
5 " " "	1.960	1.940	2.008	5 " " "	.801	.797	.828
6 " " "	1.639	1.613	1.644	6 " " "	.725	.720	.743
8 " " "	1.119	1.099	1.098	8 " " "	.576	.571	.582
10 " " "	.763	.748	.743	10 " " "	.446	.442	.446
12 " " "	.528	.518	.514	12 " " "	.342	.338	.340
14 " " "	.374	.368	.364	14 " " "	.262	.258	.259
16 " " "	.271	.266	.264	16 " " "	.201	.199	.198
18 " " "	.199	.198	.195	18 " " "	.155	.153	.153
20 " " "	.150	.148	.146	20 " " "	.120	.119	.118

The advantage of a distributed source over a point source at the same distance from the point being treated is evidently not more than 3 per cent, at any point, and really the point seems to be the better for this case as near the axis it gives a value higher by 15 per cent for 6 cm. distance. The whole advantage of the distributed source lies in this latter fact, however, since this means that the point must be farther away in order that the intensity on the axis be such as not to burn the skin near by. In other words, for the same intensity on the axis, the intensity 6, 8 or 10 cm. off the axis is 15 or 20 per cent greater for the greater

number of tubes. The field is more uniform. For the 10 cm. distance, the advantage does not appear so great.

TABLE XXVI

GAMMA RAY INTENSITIES DUE TO TWO 6 x 6 CM. PLATES, EACH CONTAINING 200 MG. IN 12 TUBES AT A DISTANCE OF 6 CM. FROM THE COMMON PLANE

DISTANCE FROM CENTER LINE	DISTANCE APART OF PLATES		
	0 CM.	4 CM.	8 CM.
1 cm.	5.209	3.934	2.758
3 "	4.819	4.033	3.058
5 "	4.033	3.943	3.442
7 "	3.058	3.442	3.554
9 "	2.167	2.669	3.185
11 "	1.493	1.910	2.494
13 "	1.034	1.318	1.789
15 "	.727	.896	
17 "	.524		
	2 CM.	6 CM.	10 CM.
0 cm.	4.590	3.278	2.238
2 "	4.553	3.414	2.402
4 "	4.299	3.677	2.823
6 "	3.677	3.708	3.288
8 "	2.823	3.288	3.451
10 "	2.013	2.566	3.113
12 "	1.390	1.838	2.445
14 "	0.962	1.269	
16 "	0.678		

Hence, absorption in the apparatus being considered, a nearly uniform field will be obtained for the primary rays at a distance of 6 cm. from the skin surface when the radioactive plates are a little less than 4 cm. apart.

TABLE XXVII

GAMMA RAY INTENSITIES DUE TO TWO 6 x 6 CM. PLATES EACH CONTAINING 200 MG. IN 12 TUBES AT A DISTANCE OF 10 CM. FROM THE COMMON PLANE OF THE TUBES

DISTANCE FROM THE CENTER LINE	DISTANCE APART OF PLATES		
	0 CM.	4 CM.	8 CM.
1 cm.	1.857	1.597	1.301
3 "	1.753	1.561	1.315
5 "	1.561	1.471	1.323
7 "	1.315	1.323	1.286
9 "	1.063	1.130	1.186
11 "	.834	.926	1.027
13 "	.644	.724	.861
15 "	.493	.561	
17 "	.378		

TABLE XXVII—CONTINUED.

DISTANCE FROM THE CENTER LINE	DISTANCE APART OF PLATES		
	2 CM.	6 CM.	10 CM.
0 cm.	1.744	1.450	1.152
2 "	1.710	1.448	1.168
4 "	1.604	1.428	1.210
6 "	1.428	1.366	1.243
8 "	1.210	1.243	1.229
10 "	.983	1.073	1.140
12 "	.777	.880	.992
14 "	.598	.696	
16 "	.458		

Hence, considering absorption in the apparatus, a nearly uniform field will be obtained for the primary rays at a distance of 10 cm. from the skin, when the radioactive plates are about 6 cm. apart.

(b) **Absorption in the Tissues.**—We may now discuss the effect of absorption in the tissues in decreasing the intensity of the radiations below the skin surface. In order to estimate the effect of absorption we may compare (1) the superficial dose, i.e., the intensity of the radiations at a given point on the surface of the skin and (2) the deep dose, i.e., the intensity of the radiations at a given point at different depths in the tissues.

Let us assume that 500 mg. of radium element screened with 2 mm. of lead and contained in 25 point sources is arranged uniformly on a plate (plane surface) 10×10 cm. and is placed so that the radium is 6 cm. distant from the surface of the skin. Let us also assume an absorption coefficient of .01 between the plate and the skin surface. The intensity at the surface of the skin on a line perpendicular to the center of the plate is then 7.19.

Under the same conditions, assuming an absorption coefficient for the tissues of .05, the intensity at a distance of 6 cm. below the surface (12 cm. from the plate) will be 1.65; 10 cm. below the surface (16 cm. from the plate) it will be .72; 12 cm. below the surface (18 cm. from the plate) it will be .57.

Under identical conditions, but assuming that the radium is placed at a distance of 10 cm. from the skin, the superficial dose (i.e., the intensity at a point on the surface) will be 2.299 while the deep dose (i.e., the intensity at a point 10 cm. below the surface or 20 cm. from the plate) will be .50.

From the above, it may be seen that, with the source 6 cm. from the surface, the ratio between the superficial and deep dose at a point 10 cm. below the surface is about 1 to 10; with the source 10 cm. from the surface, 1 to 6. The ratio of the superficial doses in the two cases is 7 to 3; the ratio of the deep doses about 7 to 5. From the standpoint of

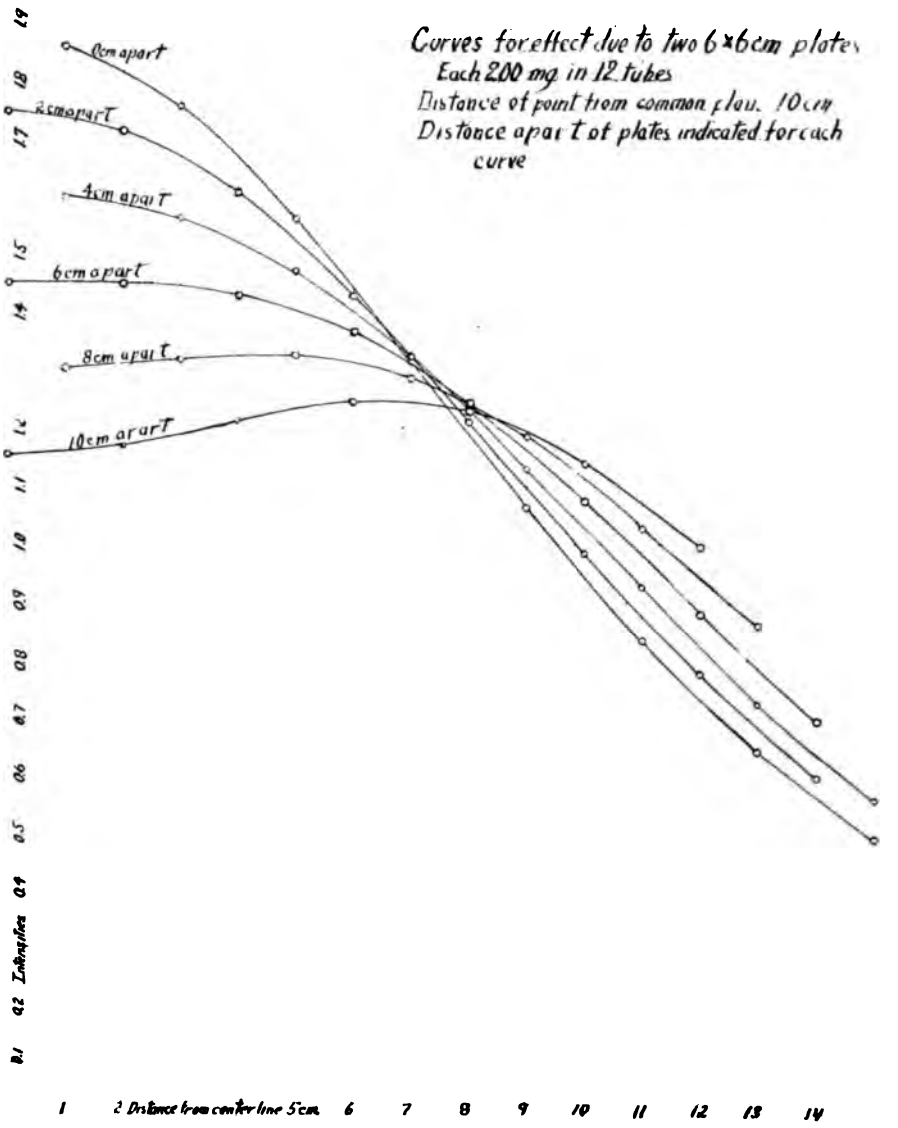


Fig. 22.—Graph illustrating Table XXVII.

equalizing the deep dose and the superficial dose, this comparison shows the advantage of placing the source at a considerable distance from the surface. Of course, the method of treatment from the greater distance has the disadvantage of requiring a larger quantity of radium or a longer exposure. It is evident that it is impossible also to put the source at a distance sufficiently great to make the superficial dose and the deep dose from primary gamma rays equal because of the absorption in the tissues. The decrease in intensity with distance from the source is also very marked. These difficulties may be minimized or overcome by using several portals of entry.

Multiple Portals of Entry

The intensity permissible at the surface, as we have already said, cannot be pushed down into the depths of the body unless more than one portal of entry be used. In order to deliver, with one portal of entry, an intensity beneath the surface approximating that at the surface, the rays should be made as nearly parallel as possible, i.e., the plate must be placed at a considerable distance from the skin. Under these circumstances, the resulting intensity at every point in the tissues is relatively low; consequently either a large amount of radium or a treatment of long duration must be used. Moreover, the absorption in the tissue, though somewhat modified by the secondary effects, is bound to diminish the intensity below the surface to a certain extent. For strictly parallel rays, the diminution amounts to from $\frac{1}{30}$ to $\frac{1}{20}$ of the total intensity per centimeter; the same, or slightly more, for rays not strictly parallel, (divergent or convergent beams). For the latter type of rays, the diminution in intensity due to the inverse square law must be taken into account; and in addition, in any case, the augmentation due to secondary rays produced in the tissues must be considered.

In order to determine the number of portals of entry necessary in a given case, one should know, if possible, the ratio between the susceptibilities of the parts that one does not wish to injure and of those that one wishes to destroy. It is then necessary to determine at what points the portals of entry can be placed; i.e., one must consider the contour of the skin surface as related to the position of the region to be treated. The only remaining requisite theoretically necessary for a complete determination of the portals of entry is a knowledge of the intensity due to the radioactive source used at given distances, above or below the skin surface.

For certain very special conditions, one can obtain the desired relations quite readily, but in the general case it is, of course, a very hard if not impossible task to find the best possible arrangement, although ordinarily one can get a usable solution and therefore one sufficient for the purpose.

Let us take, for example, a very special case. Suppose a tumor situated at a point 10 cm. below the skin is to be radiated and that we wish to treat it with radium placed at a distance of 10 cm. above the surface. To make the problem as easy as possible, we may also assume the skin surface to be a circle, having a radius of 10 cm. about the point P, which is to be treated. (Fig. 23.) It is necessary to determine the ratio of the field at S on the surface of the skin, to that at P, when a certain quantity of radium is placed at A, 10 cm. from S on the line $P\,S$ produced. If absorption be neglected and the radium be taken as a point source, the intensity at S is, from the inverse square law, $\frac{M}{A\,S^2}$ or $\frac{M}{100}$ where M is the

number of millicuries of radium emanation used. The intensity at P is similarly $\frac{M}{A\,P^2}$ or $\frac{M}{400}$, i.e., just ¼ of that at *S*.

Hence, at first sight, in order to make the intensity at *P* equal to that at *S*, one would say that it is necessary to have four portals of entry, situated at *A*, *B*, *C*, and *D*, the effects of which would all combine at *P* making the intensity at point *P* equal to that at point *S*. We find, however, four portals are insufficient since *B*, *C*, and *D* contribute not alone to the effect at *P* but also to that at *S*. Let us then try five portals. This number proves to be insufficient, and so on up to nine or more portals of entry.

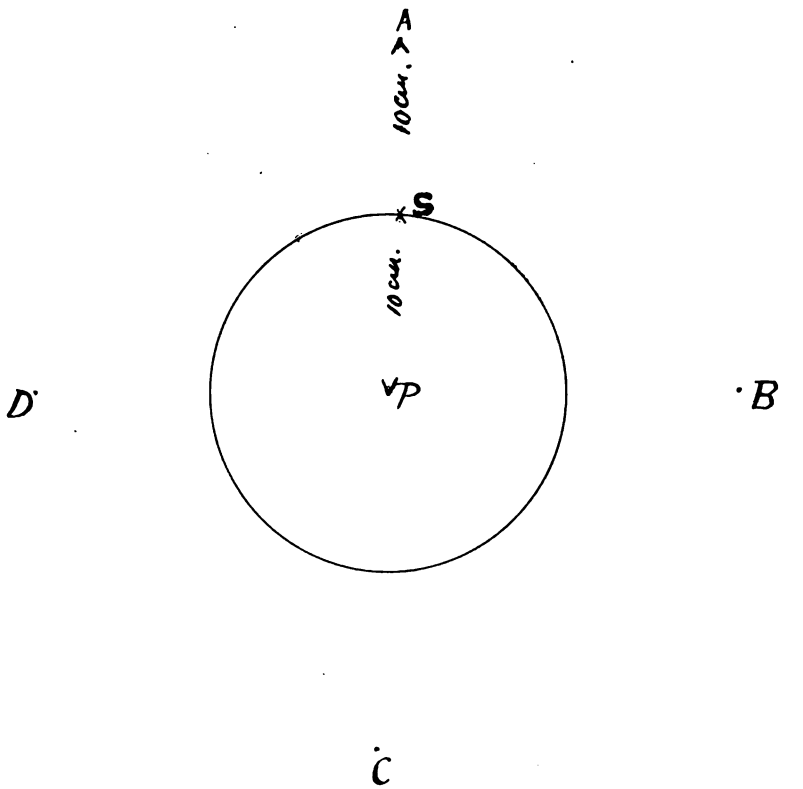


Fig. 23.—Diagram illustrating multiple portals of entry.

It should be theoretically possible, by sufficiently increasing the number of portals to obtain an intensity at *P* which would be greater in relation to that at *S* than the ratio of the carcinoma dose to the skin dose. Actually the number of portals can be made fewer by using portals outside one plane, and by suitable screening.

Let us suppose that all radiations are screened off except, for each portal, a beam just sufficient to radiate the tissue to be destroyed (assuming no sideways scattering). Then the four portals required by

theory will be enough, provided they are placed so that the overlapping of beams occurs almost entirely in the diseased tissue, i.e., the portals should not be diametrically opposite as in Fig. 23. It is then possible to place the portals much nearer together. They must be sufficiently far apart, however, so that the four beams do not overlap nearer the portals than the tumor at *P*, or even that three beams do not overlap except in the immediate vicinity of the tumor.

Let us now place an applicator containing 1000 mc., arranged on a plate (10 × 10 cm.) at a distance of 10 cm. from the skin. Let us assume that the maximum skin dose is obtained by applying it for eighteen hours, i.e., 18000 mc. 10 cm. hours (1000 × 18). Actual experiments have proved this latter assumption to be nearly correct. The maximum skin dose is thus found under the conditions stated to be 180 mc. cm. hours. $\left(\frac{18{,}000}{10^2}\right)$

Assuming the ratio of 1.15 of skin dose to carcinoma dose, as determined by Kroenig and Friedrich to be correct, the carcinoma dose that it is necessary to deliver 10 cm. below the surface at a point which we will assume to be the site of the tumor, is 156 mc. cm. hours. This dose can be delivered theoretically with four portals of entry, by giving at each portal a radiation that is slightly less than the maximum skin dose.

The above result is easily calculated from the following considerations. According to the inverse square law, the intensity at a distance of 20 cm. is ¼ of that at 10 cm.; hence in order to make the intensity multiplied by the time product at a distance of 20 cm. the same as that at 10 cm., we must use four different sites of application. The sum of the effects at each portal on the skin will then be equal to the total effect on the tumor.

The above calculation assumes that there is no absorption in the tissues. If we assume an absorption coefficient of .05, the effect due to each portal will be decreased in the deep dose by $e^{-0.5}$; hence, since the surface dose is unaffected, the number of portals of entry must be increased by $e^{0.5}$ i.e., $4\,e^{.5}$ or in other words, about 6 portals will be the number required.

It is possible, however, that the effect of "scattering" the primary beams, i.e., the effect due to secondary radiations, nearly cancels the effect of absorption.

Deep Dose Produced with X-Rays Compared with that Produced with Gamma Rays

With x-rays, the problem of delivering the deep dose is even more difficult in some particulars than with gamma rays, because of the inferior penetrating power of the former. Hence, whatever can be accomplished with x-rays can also be done with gamma rays providing the amount of radium necessary to produce the required intensities is avail-

able. If intensities at the skin surface comparable with those producible with x-rays can be produced with gamma rays, the intensities in the depths of the tissues will be far greater when radium is the source of the radiations.

It is the product of the coefficient of absorption and the intensity that really matters, however. Radium is equal or even superior to x-rays in the treatment of certain lesions involving the surface layers, because of the convenience of its applications and the closeness with which it may be brought to the points to be influenced. This nearness of application results in a more sharply bounded region being affected. There is also less penetration to points where radiation effects are not desired.

X-rays possess an advantage over radium in the fact that a parallel beam is more easily obtainable with the former.

TABLE XXVIII

RELATIVE INTENSITIES AND EFFECTS DUE TO PARALLEL BEAMS OF X-RAYS AND GAMMA RAYS RESPECTIVELY

It is assumed that the effects of the absorption of equal quantities of both agents are equal.

Assume that the absorption coefficient for x-rays=0.13; for gamma rays=0.033.

	X-RAYS		GAMMA RAYS	
DISTANCE	INTENSITY	EFFECT	INTENSITY	EFFECT
0	1	.13	1	.033
1	.88	.11	.97	.032
2	.77	.10	.93	.031
3	.68	.088	.90	.030
4	.59	.077	.87	.029
5	.52	.068	.84	.028
6	.46	.060	.82	.027
7	.40	.052	.79	.026
8	.35	.046	.77	.026
9	.31	.040	.74	.025
10	.27	.035	.72	.024
11	.24	.031	.70	.023
12	.21	.027	.67	.022
13	.18	.024	.65	.022
14	.16	.021	.63	.021
15	.14	.018	.61	.020
20	.07	.009	.52	.017
25	.04	.005	.44	.015

(1) Hence, for the same intensity at the surface, the intensity at any point below the surface is greater for gamma rays; the effect, however, is greater for x-rays down to 14 cm. depth. (2) For the same effect at the surface, however, the intensity and effects at any point below the surface are much greater for gamma rays than for x-rays.

The first of the above statements merely has to do with the relative strengths of each source to be used. The second is of importance as regards the number of sources (i.e., of portals of entry) necessary, and the

possibility of increasing the dose at points below the skin to a greater value than at the skin.

It is the ratio of the deep dose to the surface dose that determines the number of portals of entry necessary.

In order to make the dose at a depth of 10 cm., equal to that at the surface, at least four portals of entry are needed for the type of x-rays considered, while two are more than sufficient for the gamma rays. At a depth of 15 cm., eight portals of entry for x-rays, and still only two for gamma rays are necessary. Two portals will still suffice for gamma rays at a depth of 20 cm., while fifteen are needed for x-rays.

It must be emphasized that the above comparison assumes that the beams from both types of sources are parallel.

6. Secondary Radiations

Let us now consider the effect of the secondary radiations in the tissues in augmenting the intensity of the radiations below the skin surface.

It was formerly believed that the relative intensity of the rays in the depths of the tissues, as compared with the surface intensity, depended upon two main factors, viz., the diminution of the intensity with distance and the amount of absorption that the rays undergo in the apparatus and in the tissues. More recently it has been shown that in all mathematical calculations of the deep intensity, the secondary radiations resulting from the impingement of the primary radiations upon the tissues must be taken into account. Gudzent comes to the conclusion, in a consideration of this topic, that the simple absorption laws for radium rays as applied to ordinary matter cannot be applied to living tissue on account of the impossibility of estimating the secondary radiations in the latter. This author states, "it is not correct, therefore, to compare the absorption of the rays in water with the absorption in the tissues. The amount of energy that is effective biologically is always greater than can be expected according to the simple laws of absorption. According to the calculations of Glocker, with the hardest x-rays that can be technically produced, the estimated or calculated dose may be increased by the secondary radiations in the tissues at a depth of 7 cm. by 43 per cent, and at a depth of 14 cm., by 77 per cent. With the more penetrating radium rays, the percentage will be still higher. In calculations that do not consider the secondary radiations, wrong conclusions will be reached. The deep dose, on account of the reasons just stated, cannot therefore, be estimated by mathematical calculations."

Kroenig and Friedrich state, however, that the secondary radiations, produced by the impingement of primary x-rays on water approximate those produced in the tissues. Our own experiments described in Chapter VII lead us to believe that the secondary radiations in tissues may augment the effect of the primary gamma rays by as much as 70 per cent.

If this be true, it lessens materially the diminution of intensity due to absorption.

The Duration of the Exposure

Surface exposures may last from a few minutes to twenty-four or more hours. The shortest exposures are given as a rule with unscreened radium. Under such circumstances, beta and gamma rays take effect. The longest exposures are given as a rule with heavily screened radium, the gamma rays only being effective. Examples of the length of therapeutic exposures are given in a subsequent section.

The term "milligram hours" or "millicurie hours" was introduced by Dawson Turner to express the duration of the exposure. By these terms, we designate a number which is obtained by multiplying the number of mg. of radium element or of millicuries of emanation by the number of hours of exposure. We may neglect for the moment the decay of the emanation. Thus, 10 mg. or 10 mc. or emanation, employed for ten hours, would be expressed as "100 milligram" or "millicurie hours." These terms are not altogether satisfactory because of their relative inaccuracy and inadequacy. Thus the terms are without great significance, when expressing surface radiations, unless the other known factors that enter into the dose, i.e., the screening, the shape of the source and especially the distance—are also stated. A marked variation of any one of this latter group of factors alters the significance of the number of milligram or millicurie hours of exposure. For example, at a distance of 1 cm., 100 mg., concentrated at a point and applied for 10 hours will give a very different effect from the same quantity concentrated on 100 sq. cm. and applied for the same length of time. The same number of mg. hours of exposure, i.e., 1000 may be said to have been given in both instances, however.

Another element of inaccuracy consists in the fact that the quantity multiplied by the time is relatively accurate only within certain limits. Thus, at identical distances, 100 mg., contained in a minute capillary tube, applied for one hour, and one milligram contained in a similar tube and applied for 100 hours, will give different effects and yet the number of mg. hours of exposure—i.e., 100—may be said to have been given in both cases. The biologic changes in the tissues during the longer exposure are probably responsible for the difference in the observed effect.

This brings up the question of whether the biologic action is the same if one employs a large intensity for a short time or a smaller intensity for a longer time. According to Kroenig and Friedrich's experiments with x-rays, if the ratio of intensities employed is equal to 1 to 5 the degree of a biologic action for the same dose is independent of the intensity. For ratios greater than 1 to 5 the degree of the biologic action for the same calculated dose is greater for the greater intensity. Accord-

ing to these authors, therefore, if we assume this statement to hold for radium, it may be roughly estimated that 20 mg. applied for ten hours would give approximately the same biologic effect as 100 mg. applied for two hours, provided the other conditions of the application are identical. In both cases, 200 mg. hours would be the calculated dose. On the other hand, 20 mg. applied for ten hours would give a less intense effect than 200 mg. applied for one hour, although in both cases the dose may be stated to be 200 mg. hours. Practical experience has shown that the biological effect is not the same for large variations of the time and intensity. It should be possible, however, to determine more accurately the biologic effect of variations of these two factors by a sufficient number of experiments. "The physiological effect of the radiation must depend largely but not entirely upon the total ionization produced during the treatment per unit volume of tumor, which is substantially a measure of the energy absorbed. It is evident then that the intensity of radiation at the point we want to affect and the time of exposure are equally important. But we can produce the same total ionization by a small intensity of radiation and a long exposure or vice versa and the question is whether it makes any difference physiologically which method we use.

"For small variations, it makes no appreciable difference if the time of exposure is increased in the same proportion that the intensity of radiation is decreased or vice versa. But if we increase the intensity 100 times and decrease the time 100 times we cannot expect to obtain the same result as before. Apparently then there is an optimum intensity of radiation coupled with a definite time of exposure but, unfortunately, the relation between the two varies with the nature of the tumor, etc., and cannot be determined except by experience." (Failla.)

In spite of their limitations and relative inaccuracies we believe that the expressions "milligram" and "millicurie hours" serve a useful purpose and should not be discontinued. When these terms are used, however, the other factors already mentioned that are of importance in estimating the dose should also be stated. As the third factor of most importance is usually the distance of the source from the surface, I would suggest that in the use of the terms "milligram" and "millicurie hours," the distance in centimeters be stated. Thus, one may say, 100 milligram-centimeter-hours or 100 milligram-10 centimeter-hours, the first expression meaning that at a distance of one centimeter and the second that at a distance of 10 cm., 100 mg. hours were given.

Millicurie Hours

While the number of "milligram hours" may be easily found by multiplying the number of mg. used by the number of hours of exposure, the problem is not so simple when one wishes to compute the number of "millicurie hours," on account of the decay of the emanation, which

loses approximately 16 per cent of its activity each twenty-four hours. It is of importance, therefore, to determine the amount of emanation with which it is necessary to start a given interval (treatment) in order to have a given mean value during that interval. This is shown in Table XXIX.

TABLE XXIX

TIME OF APPLICATION IN HOURS	VALUE, I.E., NUMBER OF MILLICURIES NECESSARY TO START WITH IN ORDER TO HAVE MEAN VALUE OF 100
1	100.4
2	100.75
3	101.1
4	101.5
5	101.9
6	102.3
7	102.65
8	103.0
9	103.4
10	103.8
11	104.2
12	104.55
13	104.95
14	105.3
15	105.7
16	106.1
17	106.5
18	106.9
19	107.3
20	107.7
21	108.1
22	108.5
23	108.9
24	109.3
30	111.6
36	114.2
42	116.5
48	119.1

In most cases it is sufficient to take the reciprocal of the value which the strength will take at the middle of the period of application. Thus for 48 hours to take

$$\frac{100}{\text{value present 24 hours later}} \text{ i.e., } \frac{100}{e^{-24(.007506)}}$$

$$\text{or, approximately, } \frac{100}{5/6} = 6/5 \times 100 = 120$$

This holds more accurately for a shorter period, less accurately for a longer one.

We may now give a few illustrations of dosage.

1. Superficial Radiations

Radium Salts in Plaques.—For many skin diseases, ¼ strength applicators may be used. It is convenient to have four applicators which may be laid side by side to form an area of 16 square centimeters. The total quantity of radium element in the four applicators is thus 20 mg. With this type of apparatus, a caustic dose may be easily and even inadvertently given if no screen is used and the time of application unduly prolonged. For the most superficial effects, one may give an exposure, if the apparatus is unscreened except for the rubber dam in which it is wrapped, of from three to five minutes. Such exposures should not be repeated more than two or three times in the course of a week.

Such treatments are adapted to superficial skin diseases.

For skin disorders that are somewhat infiltrated and require deeper effects, the apparatus may be screened with 0.1 mm. of lead and an exposure of from one to four hours in several periods may be given.

For the production of still deeper effects, the apparatus may be screened with a layer of lead 1 mm. thick and an exposure of six or more hours in several periods may be given. In all the above exposures, the apparatus may be applied in close contact with the skin. If the screening is 2 mm. of brass and the distance from the skin is increased to 1 cm., an exposure of forty-five hours in three periods may be given.

Radium Salts or Emanation in Tubes.—For superficial effects, 50 mg. or mc. may be concentrated on an area of from 4 to 6 square cm. The screening may consist of a layer of silver .5 mm. thick plus a layer of rubber 2 mm. thick. An exposure of from three to four hours may be given, when small areas such as from 4 to 6 square cm. are treated.

For the production of somewhat deeper effects, the screening may be increased to 1 mm. of silver plus 1 cm. of rubber or wood. An exposure of twelve hours or more may be given when small areas such as 4 to 6 cm. are treated.

2. Deep Radiations

For deep effects, plaques or tubes containing radium salts or tubes of radium emanation may be used. For influencing deeply seated tumors, exposures lasting from ten to thirty or more hours in periods of ten or more hours each are suitable.

The radium plaques or tubes may be arranged side by side on a plane surface having, e.g., an area of 100 square cm.

The routine screening in these treatments is 2 mm. of brass or its equivalent of another metal. The radium is placed at a distance of from 6 to 10 or more cm. from the skin surface. The use of not less than 500 mg. or mc. is necessary in most cases; in other cases not less than 1000 mg. or mc. should be employed. If 500 mg. or mc. are used, a

total exposure of 25 hours at a distance of 6 cm. may be given in two or more periods. At a distance of 10 cm., a total exposure of 36 hours may be given in two or more periods. With 1000 mg. or mc. under the same conditions, 12½ hours may be given at a distance of 6 cm.; 18 hours at a distance of 10 cm. If emanation is used, due allowance must be made for its decay. The exposures may be given in two or more periods.

INTRATUMORAL RADIATIONS

In some cases, as has been said before, the radioactive material may be inserted directly into the tumor tissue. Radium salts in metal needles may be used for this purpose or radium emanation contained in metal needles or glass ampoules may be employed. I usually prefer radium emanation in glass ampoules.

At the present time, the exact dosage employed in metal needles is largely a matter of experience and judgment on the part of the operator. Speaking very generally, 5 steel needles having a wall thickness of 0.4 mm. and each containing as much as 10 mc. of emanation may be

TABLE XXX

SUGGESTING DOSES (JANEWAY) THAT MAY BE USED WHEN BARE EMANATION AMPOULES ARE INSERTED INTO TUMORS

FOR CIRCULAR AND APPROXIMATELY OVAL TUMORS OF THE SAME LONG DIAMETER

DIAMETER	DEEP INFILTRATION	SURFACE AREA	DOSAGE
1 cm.		.77 sq. cm.	5 mc.
1½ cm.		1.7 " "	8 "
2 cm.		3.14 " "	10 "
2½ cm.	Not more than 1½ cm.	4.8 " "	15 "
3 cm.	Between 1 and 2 cm.	6.5 " "	17.5 mc.
4 cm.	Between 1 and 2 cm.	12.5 " "	20 "
5 cm.	Between 1 and 2½ cm.	19.3 " "	22.5 "
6 cm.	Between 1 and 3 cm.	28.27 " "	25 "

FOR SPHERICAL TUMORS THERE IS LITTLE DIFFERENCE

DIAMETER	AREA OF PLANE OF DIAMETER	NO. OF CUBIC CENTIMETERS	DOSAGE
1 cm.	.77 sq. cm.	.52 c.c.	5 mc.
1½ cm.	7.7 " "	1.70 "	8 "
2 cm.	3.14 " "	4.18 "	10 "
2½ cm.	7.8 " "	8.19 "	15 "
3 cm.	6.5 " "	14.08 "	20 "
4 cm.	12.5 " "	33.44 "	22 "
5 cm.	19.3 " "	65.29 "	25 "
6 cm.	28.27 " "	112.86 "	30 "
7 cm.	38.48 " "	251.52 "	35 "
8 cm.	50.26 " "		40 "

left in the tissues six hours. In all cases needles should not be inserted nearer to each other than 1 to 2 cm. Prior to Bagg's experiments, which have already been referred to, the dose used in the insertion of the glass emanation ampoules was larger than we now employ. This author's experiments have shown the advisability of using relatively small doses.

In dealing with smaller growths, it is sometimes advisable to increase the dose suggested by Bagg. We frequently employ in treating the smaller growths 5 mc. of emanation per c.c. of tumor tissue. This amount of emanation may be contained in several ampoules. When treating the larger growths, 0.5 mc. per c.c. of tissue may be sufficient, when the total amount of emanation equals from 25 to 30 mc. When the latter quantity of emanation is used, a larger amount of "cross firing" from the different tubes naturally takes place than when smaller quantities of emanation are employed.

Methods of Decreasing and Increasing the Radiosensibility of Tissues.—The question naturally arises whether it may be possible especially in deep therapy to make the skin more insensitive and the tumor more sensitive to the radiations. Schwarz has demonstrated that the radiosensibility of the skin is dependent to some extent on its plethora. In order to create an anemia of the skin and thus render it less sensitive, this author used compression of the surface by thin wooden plates and showed that the skin was able to stand without injury doses of radium that otherwise injured it. H. E. Schmidt and others have confirmed this observation. Reicher and Lenz have suggested that a diluted adrenalin solution be injected into the skin in order to render it anemic. Christoph Mueller-Immenstadt has used high frequency currents for the same purpose. He states that this procedure not only desensitizes the skin, but renders the underlying tumor more sensitive because of the coincident plethora produced in the tumor. This observation has not yet been confirmed. Several authors have endeavored to sensitize tumors by means of injections of different chemicals, such as eosin, etc. Werner injected lecithin and cholin into tumors for the same purpose. The injection of the various substances just named has not led, however, to any practical results. Gauss and Lemcke, Mueller-Immenstadt and others have suggested that by injecting into tumors substances of high atomic weight, such as electrocuprol, cuprose, etc., the formation of secondary rays in the tissues might be increased. Halberstaedter and Goldstuecker radiated trypanosomes which had been immersed in colloidal metal solutions and showed that they had become more sensitive to radiations than the controls which were immersed in salt solution.

It is hoped that future researches may widen the scope of these experiments. Up to the present time, however, the attempts at desensitizing the skin and sensitizing the tumor have not proved of any utility in actual practice.

CHAPTER XIV

THE TECHNIC OF RADIATION

It is manifestly impossible to give a complete description of all of the methods of applying the apparatus for the various objects of radiation. We may, therefore, limit ourselves mainly to a discussion of the different principles involved.

It is important that the operator should have the requisite knowledge of the amount of radium in the apparatus, the quantity and quality of the rays passing through the screens, and the effect on the skin at the given distance.

There must also be a clear understanding of the object of the radiation. The kind of tissue that is to be treated or destroyed together with its situation and extent must be known as far as possible.

(a) SURFACE RADIATIONS

1. Superficial Radiations

The lesion to be treated, if superficial and on the skin, may be gently cleansed if necessary and the rubber, wood, gauze or other material of

Fig. 24.—This photograph shows the method of handling radium. A radium tube is being inserted into a screen.

the thickness required in order to keep the radium at the proper distance may then be applied and held in place by adhesive tape or a bandage.

The radium plaques or tubes, singly or in combination, may then be laid upon the material covering the lesion and held in position in the same way.

Protection from the discharges from a moist lesion is always assured for the apparatus by wrapping it in a finger cot or dental rubber dam.

In the treatment of a lesion of the mucous membranes, the tubes may be attached to a wire or other carrier, covered with the desired thickness of rubber or gauze and then, after being encased in a finger cot, applied directly to the lesion. In order to protect the normal tissues adjacent to a lesion on the skin, one may use a sheet of lead 2 to 4 mm. thick in which an aperture is cut to fit the lesion. This lead absorbs 8 to 15 per cent of the gamma rays and while it does not, of course, protect the normal tissue completely, it affords a relative amount of protection that is ordinarily sufficient. It must be remembered that if the radium

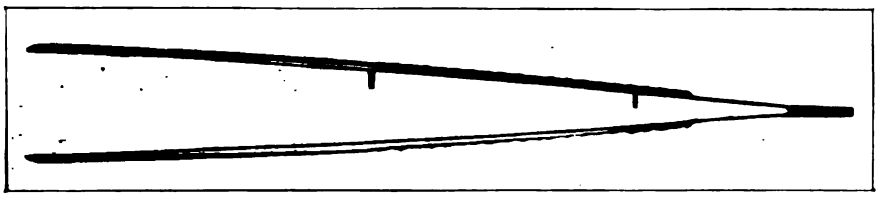


Fig. 25.—Forceps 30 cm. long for handling radium tubes.

tube is held at a distance of several millimeters from the lesion by the lead protector, this distance must be taken into consideration in estimating the dosage. In accordance with the law of inverse squares, the intensity of the rays from a single tube diminishes very rapidly as the distance of the tube from the lesion increases.

For the relative protection of the eyeball in epithelioma of the eyelid, we use a specially constructed gold screen, made after the model of an artificial eye. It is always desirable if possible to protect hairy regions, such as the eyebrow, from the action of the rays.

For applications to the different natural cavities of the body, various methods may be used to suit the requirements of the case.

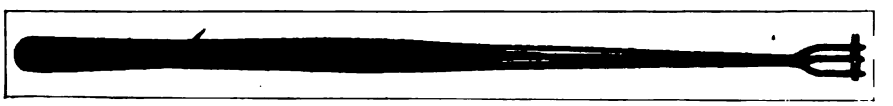
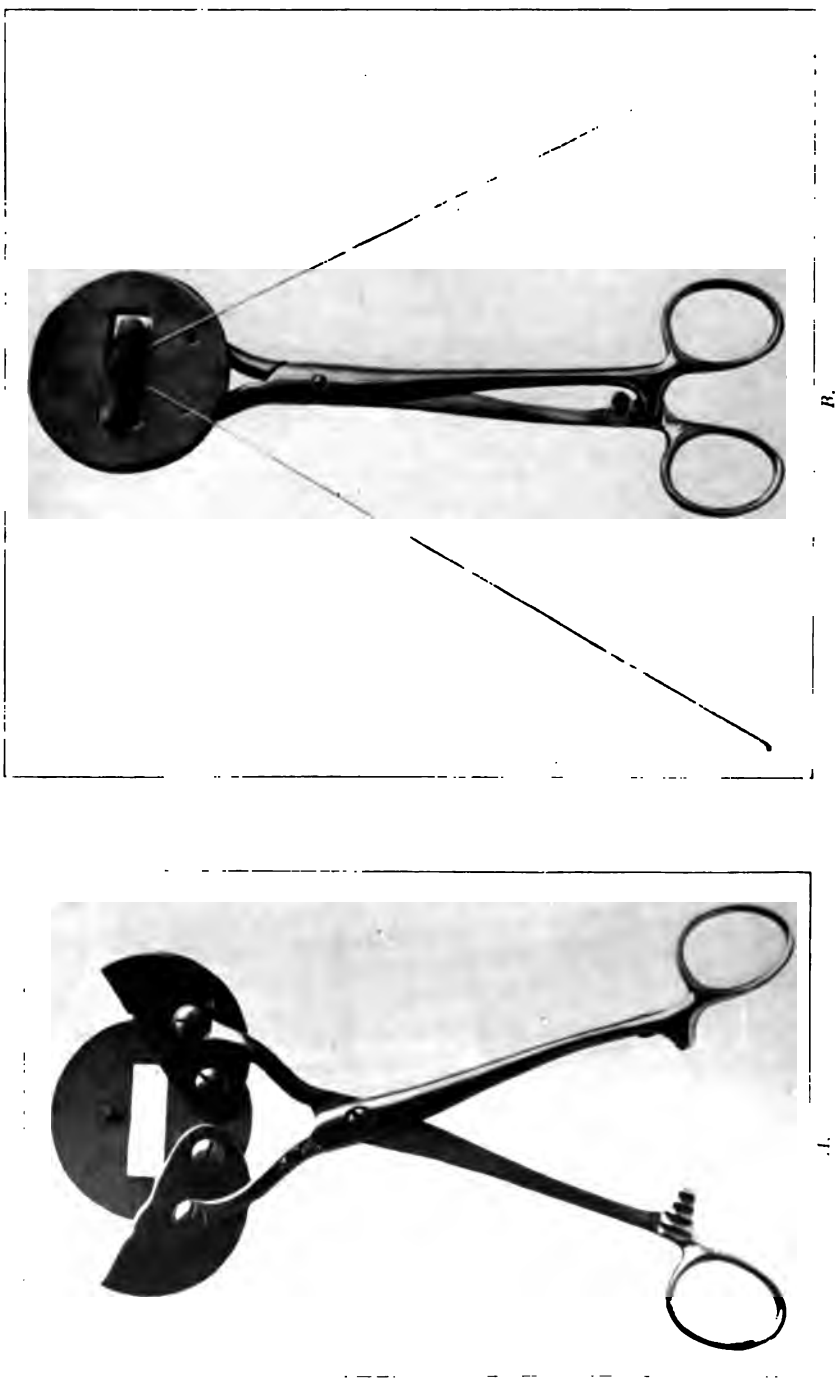


Fig. 26.—Three pronged forceps 30 cm. long for handling radium tubes.

In the vagina or uterus, gauze packing suffices as well as anything for holding the tubes in position. Heavily screened tubes placed against the cervix will not ordinarily injure the healthy adjacent vaginal mucous membrane if sufficient packing is used to separate the walls of the vagina to the fullest extent. "Distance" in addition to the screens on the radium protects the healthy tissue sufficiently.

In the nose, mouth, esophagus, rectum and bladder, the tubes may be attached to a pliable silver wire which can be bent to the required angle and fastened to the adjacent skin. In addition to the wire it is always advisable to have the radium tube anchored by a long silk thread which is



B.

A.

Fig. 57.—Author's forceps for wrapping radium tubes in rubber dam. *A*, Forceps open. With this forceps, the technician may wrap and tie the radium tube without touching the tube with the fingers. *B*, Reverse side of forceps closed.

also fastened to the neighboring skin by adhesive tape. This procedure is a precautionary measure in case the wire should break.

For the protection of the rectal wall opposite to a circumscribed carcinoma of the organ, we insert a finger cot which may be distended with air by a catheter. In this case, also, distance protects the healthy, ballooned out, mucosa.

For some years, especially in mouth cases, we have made use of the dental modeling compound suggested by Janeway. This material can be fashioned to suit the outline of any growth that is accessible and the tubes may be laid in little troughs in the compound. By this device,

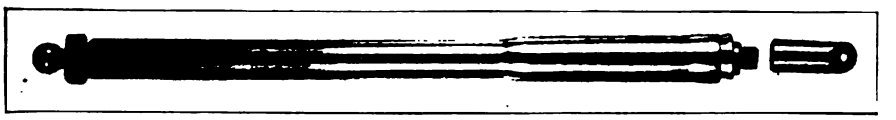


Fig. 28.—Screen holders. These instruments are of two different sizes and enable the technician to grasp the cylindrical screens containing the emanation tubes. One end of a screen is shown inserted into the holder. A similar holder (not shown in the photograph) grasps the other end of the screen. The technician may thus screw the two parts of the screen together, without allowing the fingers to come in contact with the radium tubes.

the tubes may be held in position without much discomfort to the patient for the required length of time.

The amount of radium to be used in superficial treatments naturally varies with the purpose of the radiation.

For example, if a tumor is very small and superficially situated on the skin, a plaque of radium containing as small a quantity as 10 mg. may sometimes be used. The beta rays from such a plaque may be utilized by employing little or no screening. The plaque may be placed in direct contact with the lesion or at a distance of a few millimeters from it.

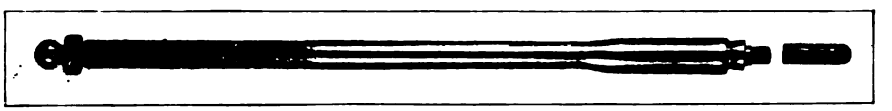


Fig. 29.—Same apparatus as in Fig. 28 but of smaller size.

When dealing with larger superficial growths on the skin 200 or more milligrams may be required. The radium may be contained in plaques or tubes that are screened with 1 mm. of silver or its equivalent and may be separated from the lesion by 1 cm. of rubber or wood.

For epithelioma of the mucous membranes, it is seldom wise to use less than 200 milligrams of radium element or mc. of emanation.

In using the technic suggested above, more or less local inflammatory and even destructive action may be produced by the radium, although certain lesions may retrogress without macroscopic evidences of inflammation.

The biologic effect of the radiation naturally depends on the technical

conditions of the application, i.e., the quantity of radium, the shape of the applicator, the screening, the distance and the duration of the exposure.

The frequency of repetition of superficial treatments depends, of course, on the dose employed. Exposures may be given daily or on alternate days or twice weekly, etc., depending on all the circumstances.

Fig. 30.—Flat silver screens with caps, devised for holding from 2 to 6 enamel emanation tubes. These screens are 2 cm. long, 4 to 16 mm. wide (outside dimensions), and vary in wall thickness from 0.5 mm. to 1.5 mm.

2. Deep Radiations

In postmortem examinations of cancer of the cervix which had been treated by placing radium in or against the cervix, Bumm found that cancer cells were destroyed up to a distance of 2½ to 3 cm. from the radium tube. At a distance of 4 cm., vigorous carcinomatous cells in groups as large as peas or cherries were found in the parametrium. Beyond 5 cm., cancerous lymph glands were found that were not affected. As a result of these observations, Bumm's dictum that radium has an effective area of influence of not more than from 2 to 3 cm., was widely accepted.

According to the earlier observations of Wickham and Degrais, radium rays may penetrate effectively to a depth of at least 9 cm.

Kroenig has recently stated that it is possible to radiate successfully a carcinoma of the cervix uteri through the abdominal wall, i.e., the

rays penetrate effectively to a depth of at least 10 cm. Kelly and Burnham and many others have successfully radiated mediastinal and abdominal tumors. In such cases it may be estimated that the rays penetrate to a depth of at least 10 cm.

Kroenig and Gauss have stated that the rays from 500 mg. of radium element that is distributed on a plate apparatus placed at a distance of 6 cm. from the skin may penetrate effectively to a depth of from 14 to 16 cm. It is evident that Bumm's dictum, that radium rays will not penetrate effectively into the tissues to a distance of more than from 2 to 3 cm., must be given up. Under certain conditions, such as existed in Bumm's cases, his conclusions were undoubtedly correct. For example, in the treatment of cancer of the cervix uteri, even though the quantity of radium be very large and the duration of the treatment prolonged, the

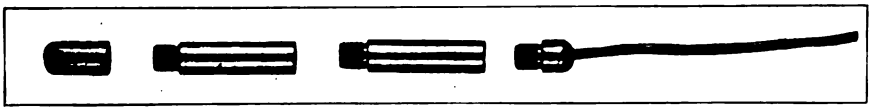


Fig. 31.—Tandem gold screens for holding one or more enamel emanation tubes. These screens have a universal thread so that a radioactive rod of any desired length may be made. The proximal end of the apparatus is attached to a long flexible silver wire. Length of each screen 2 cm., outside diameter 4 mm., wall thickness 0.8 mm.

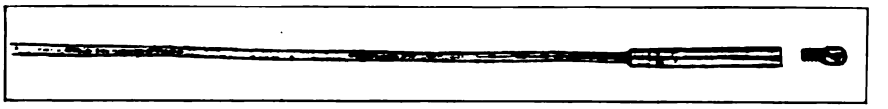


Fig. 32.—Platinum screen for containing a glass emanation tube. A long silver wire is screwed into the end of the screen so as to facilitate its introduction into small cavities. Length of platinum screen 2 cm., outside diameter 2 mm., wall thickness 0.5 mm.

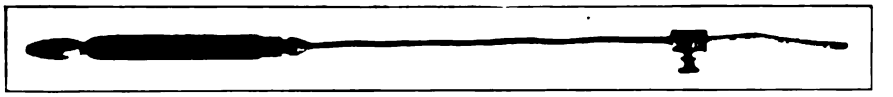


Fig. 33.—Screen for inserting radium tubes into the esophagus. The bulb on the distal end may carry a silk thread for guiding the instrument. A "screw-nut" slides on the wire so that the distance from the applicator to the patient's teeth may be easily maintained.

effective raying of distant cancerous masses by means of a tube placed within the cervix may be practically impossible. Long before cancer cells situated near the walls of the bony pelvis, (i.e., about 6 cm. distant from the tube) would be seriously affected, an enormous overdose would be given and a dangerously destructive action might be produced on the tissues adjacent to the tube.

On the other hand, if a quantity of radium sufficient to give an adequate intensity is properly distributed on a plane surface of sufficient size and is placed at a sufficient distance from the lesion, the depth to which the rays will effectively penetrate without untoward effects may be enormously increased. There is abundant evidence that indicates, as has been shown in the previous chapter, that by this method of pro-

cedure it is possible to radiate any part of the body with an intensity of rays powerful enough to destroy malignant cells, however deeply situated. By using different portals of entry, almost any part of the body may be brought, for purposes of radiation, within a distance of from 10 to 14 cm. from the surface of the skin. The limitations of radium therapy, therefore, are not those imposed by the inability of the rays to penetrate with an adequate intensity to a sufficient depth, but rather by the fact that serious injury to normal structures may be caused by the delivery of too large a dose of deep rays. It must be especially

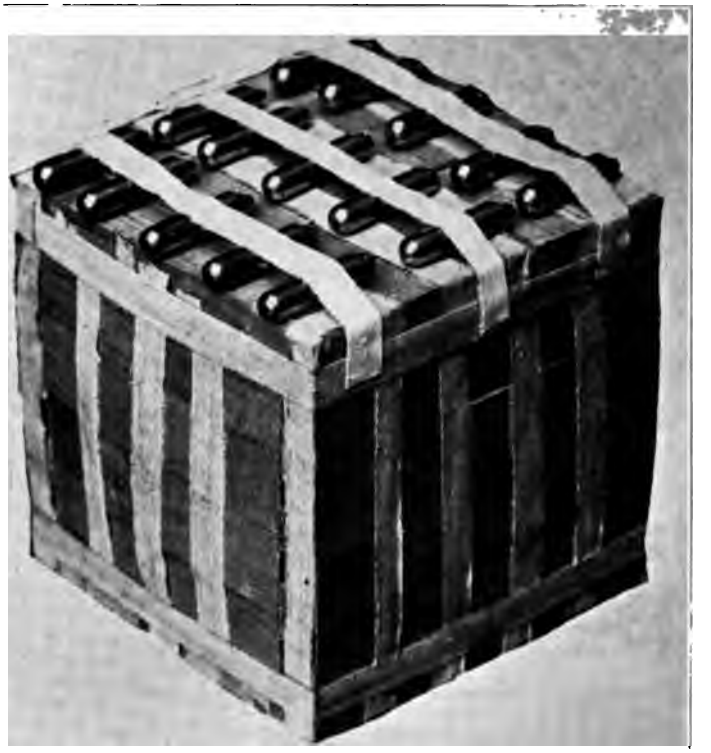


Fig. 34. Radium pad composed of "squares" of soft wood. The interior of the package is stuffed with cotton. Dimensions of pad 10×10×10 cm. Fifteen screens containing radium emanation tubes are held in position on the pad by adhesive plaster. This type of apparatus is used for deep gamma radiation of large tumors.

emphasized that, for adequate deep effects, a considerable quantity of radioactive material must be used preferably not less than from 500 to 1000 or more milligrams of radium element or millicuries of emanation. In some cases, 2000 mg. or mc. are desirable. While the relatively slight intensity from smaller quantities, such as 300 milligrams, can be to some extent compensated for by prolonging the exposure, practical experience has shown that in most cases the best effects are obtainable only by using the larger quantities for a shorter time.

For the treatment of deeply seated tumors or other pathologic tissues, when the overlying skin or mucous membrane is to be preserved, pads or packages of various sizes are used in order to give the desired distance. These pads are made up in advance to suit the individual case by using a number of small square blocks, made of soft wood, balsa wood, cork or hard rubber. A suitable size for these blocks is $2 \times 2 \times 1$ cm. The blocks may be fastened together by adhesive tape to form various sized

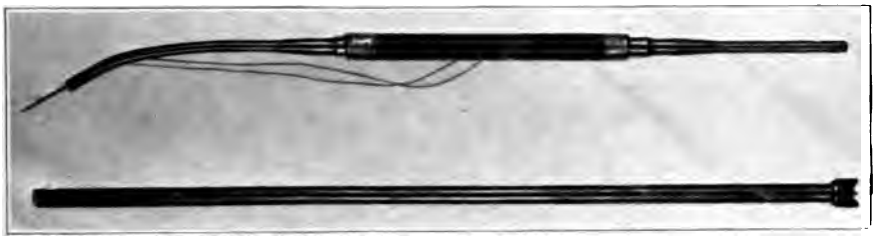


Fig. 35.—The upper photograph shows the needle holder devised by Dr. O. T. Freer. A metal needle containing a glass emanation tube is shown in the end of the holder. After insertion into the tumor tissue, the needle may be withdrawn when the required exposure has been given. The lower photograph shows the instrument devised by Dr. Freer to facilitate the withdrawal of metal needles from tumor tissue. The silk ligature attached to the needle may be engaged in the groove on the end of the instrument. Traction on the needle may then be easily made without damage to the tissues.

packages. On account of the joints formed by the tape, even the larger pads have a certain degree of flexibility. On these packages or pads the tubes are placed in parallel rows or in accordance with any desired arrangement. The tubes may be held in place by strips of adhesive tape.

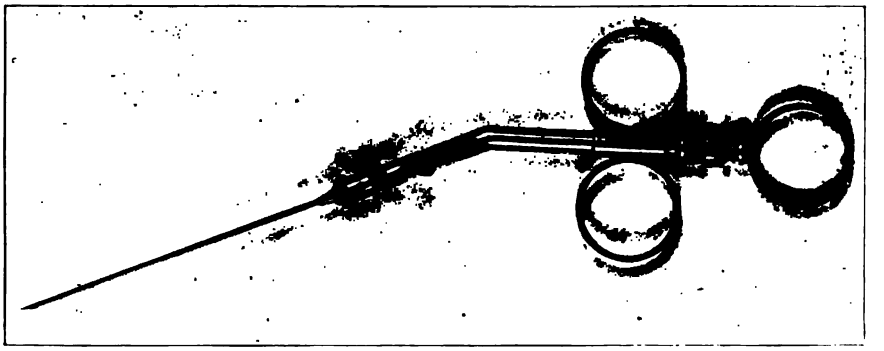


Fig. 36.—Author's instrument, constructed on the plan of an ordinary syringe, for burying emanation ampoules. The obturator, sliding in the lumen of the needle, enables one to eject the ampoule into the tumor tissue.

The size of these large packages varies in accordance with the lesion to be treated. We frequently use packages having the dimensions of $6 \times 6 \times 6$ cm. or $10 \times 10 \times 10$ cm. (See Fig. 34.) In order to reduce the weight of the larger wooden packages and to minimize the amount of gamma ray absorption in the applicator, we fill the center of each package with cotton, the small wooden blocks forming merely the outside or shell of the package. In applying the packages carrying the radium, the so-called "cross

fire'' method suggested by Wickham should be utilized to the utmost. In accordance with this principle, subcutaneous tumors are attacked from as many different angles or sides as possible, in order to deliver the greatest possible volume of rays to the deeper parts of the growth and at the same time spare the overlying skin. The periphery of a tumor is always attacked first. As we have pointed out in the previous chapter,

Fig. 37.— Heavy cast-iron movable shield for the protection of the operator.

in order to produce a uniform field of radiation at the skin surface, the radium packages in which the radium is 6 cm. from the skin should be 4 cm. apart; if the radium is 10 cm. from the skin the packages should be 6 cm. apart. Otherwise some sort of a shield should be used in order not to give an overdose to a single skin area.

If large and deeply seated tumors, such as may occur in the neck,

breast, abdomen, pelvis, etc., are present, there should be used for the radiations not less than 500 to 2000 or more milligrams or millicuries. The radium should be placed at a considerable distance, e.g., ten or more centimeters from the skin. The tubes or plaques may be evenly arranged according to the desired method of distribution on one side of the wooden package just described. The opposite side of the package is placed on the skin. All of the requirements of proper distribution of the radium, its distance from the skin, etc., may thus be fulfilled. In addition, every area of skin from which the tumor can be attacked should be homogeneously radiated as we have just described.

By this method of procedure, a deep gamma ray effect is produced, but there is little or no local inflammation of tissue next to the applicator, if the duration of the exposure is correct.

Employing 1000 mg. distributed over an area of 100 sq. cm. and placed at a distance of 10 cm. from the surface, the safe limit of skin toleration is about 18 hours. If 2000 mg. are used, 9 hours may be given. This exposure may be divided into two or more periods. An interval of several days should elapse between each period.

It must be emphasized that the above dosage cannot be repeated with impunity because of the deep effects on normal tissue. A second course of treatment, given six weeks later, should not consist of over 5000 mc. or mg. hours. These doses were suggested by Janeway and Failla and they accord in a general way with my own practice.

In using adhesive plaster to bind the radium packages to the skin, it must be remembered that the epidermis that has been rayed heavily is unusually sensitive. Superficial excoriations may easily occur and may become a source of great annoyance to the patient. Great care should be employed therefore in applying and removing sticking plaster in such areas.

(b) "INTRATUMORAL" RADIATION

(1) The insertion of radium salts or radium emanation in metal needles into the tissues.

In the use of metal needles the following precautions should be observed: (1) An aseptic technic is necessary inasmuch as screened radium does not have a marked antiseptic effect. (2) Several needles of moderate strength should, if possible, be used, rather than one strong needle, in order that an even distribution of the rays may be produced in the entire growth. (3) It is important that a certain quantity of healthy tissue should surround the growth in order that repair may be accomplished. (4) The quantity of radium embedded in a growth depends upon the size of the tumor and the thickness of the needle wall and to some extent upon the situation of the growth. Encapsulated organs, such as the tonsil and

the prostate, are especially suitable for needling. The needles should not be inserted into normal tissue.

(2) The insertion of bare glass ampoules containing radium emanation into the tissues.

The method of treating tumors by the insertion of bare glass emanation tubes or ampoules is one of considerable promise. Indeed it is not too much to say that this method has almost revolutionized the treatment of certain localized tumors. The method appears to have been suggested first by Duane. It has been employed extensively by Janeway and his coworkers at the Memorial Hospital in New York, by Kelly and his associates in Baltimore, by the writer and many others.

The glass emanation ampoules that are used are ordinarily about three millimeters long and 0.3 mm. in diameter. They may be inserted into the tumor in proper cases and allowed to remain *in situ*. Over 90 per cent of the activity is lost in two weeks and they decay practically to zero in about forty days. Each tube during the entire time of decay gives a dose that may be expressed in millicurie hours by multiplying 132, i.e., 5½ days, by the number of millicuries originally in the tube. We assume in the foregoing calculation that the tube has not been broken during the insertion and that it remains in the tissues until its complete or nearly complete decay. It is advisable to combine in some cases the insertion of the emanation ampoules with powerful surface gamma ray radiations.

In the introduction of the ampoules, the following technic suggested by Failla may be used: The glass emanation ampoules may be boiled and inserted into the sharp end of a sterile needle which admits a plunger at the other end. It is convenient to have at hand a number of needles, each of which is loaded in this manner. After insertion into the tumor tissue, the needle should be withdrawn a few millimeters just before the plunger ejects the ampoule so that the danger of breaking the ampoule by forcing it against the tissue is obviated. One may also withdraw the needle simultaneously with the pushing in of the plunger. The ampoule thus rests in the minute cavity formed by the sharp end of the needle. I have devised a small instrument, which has been previously mentioned, for the insertion of the ampoules. (Fig. 36.)

While theoretically some slight danger of inducing metastasis or transplanting tumor cells may be incurred by this method, I am of the opinion that this danger is negligible if the technic is correct.

The following suggestions may be observed in the insertion of the [illegible]:—Aseptic precautions must be used; each ampoule should not contain more than three millicuries of emanation; the ampoules should be inserted about one cm. apart; care should be taken not to implant [illegible] large vessels, nerve trunks, bones or thin-walled viscera; if

possible to avoid it, the ampoules should not be inserted into healthy tissues.

A zone of necrosis forms around each ampoule a week or more after its insertion. Healing occurs in from four to eight weeks and in favorable cases a smooth cicatrix is left.

The quantity or dose of radium emanation to be used in intratumoral radiation is considered in the Chapter on Dosage.

It must be especially emphasized that the effects of radiation resulting from the introduction of radioactive substances into tumors are strictly localized. The method is evidently not suited for the treatment of large, deeply situated lesions. Such lesions must usually be attacked by the method of deep gamma ray radiation that has already been described.

In some cases, the two methods, intratumoral radiation and deep gamma radiation, may be advantageously combined.

CHAPTER XV

RADIUM IN GENERAL SURGERY

A. MALIGNANT TUMORS

Carcinomata exhibit different degrees of radiosensibility. Adler has tried to determine whether this difference in sensibility depends on the histologic structure of the tumor. According to this author's investigations, rapidly growing carcinomata of the primary glandular type are almost refractory to radium while with the sclerotic types developing more slowly excellent results are frequently obtained. Bumm and Schaefer on the other hand have found that the so-called medullary carcinomata, in which the supporting stroma is scanty, are more easily influenced by radium than the sclerotic types. According to these authors no carcinoma has been observed that can resist radium. Kroenig and Friedrich also state they have found that every carcinoma can be influenced by radium if it is applied in the correct technical manner. They point out, however, that a difference in effect is to be observed in noncachectic and cachectic individuals. The former class of patients usually responds well, while in the latter class, heavy radiations may be ineffective or even dangerous. On this account these authors would exclude markedly cachectic individuals from treatment by radiations. In this view they are supported by Gudzent. Klein has shown that in the tissues surrounding carcinoma there is a so-called battle zone consisting histologically of advancing carcinoma cells opposed by leucocytes and connective tissue cells. In cachectic individuals, this zone is scarcely to be found, although the carcinoma may be advancing rapidly.

From the clinical point of view, practically all observers agree that carcinoma in individuals who are in a relatively robust condition is much more susceptible to radiations than carcinoma occurring in the cachectic. We have seldom seen even good temporary results in those who exhibit considerable cachexia.

Summing up the different views, we may conclude, in spite of some opinions to the contrary, that all accessible carcinoma is probably more susceptible to proper doses of radiation than most normal tissues. There is little doubt, however, that carcinomata of different and even of the same pathologic types exhibit considerable variation in their response to radium. Whether this depends altogether upon some difference in the radiosensibility of the tumor cells, it is impossible at present to decide. The writer believes that the radiosusceptibility of the growth is the most important factor. Other factors, however, in all probability are also at work in determining the response of the tumor to radiations.

(a) Operable Malignant Tumors

Janeway has raised the question of the advisability of treating primarily with radium certain cases of cancer of the mucous membranes even though they may be operable. Gudzent states that it is justifiable to treat with radium selected cases of operable carcinoma provided the necessary surgical experience and an adequate knowledge of the technic of the application of radium can be combined. In cancer of the cervix uteri, even though it is operable, Bumm, Doederlein and Kroenig have abandoned operation in favor of radium therapy. Nearly all radium therapeutists are in accord, however, that with the exception of certain selected cases of epithelioma of the skin, and mucous membranes, operable growths should be operated upon.

We have already mentioned that a certain type of malignant tumor in mice frequently cannot be successfully transplanted after radium treatment. The most rational procedure, therefore, even in dealing with clearly operable malignant disease is first to treat the growth and the lymphatics draining the involved area with radium. Immediately afterward, operative removal of the tumor should be carried out. A few weeks later, postoperative prophylactic radiations should be given.

(b) Inoperable Malignant Tumors

In inoperable cases of malignant disease, treatment with radium has been followed in numerous cases by a clinical recovery that has sometimes been maintained for a number of years. Radium, therefore, gives promise at least of a certain amount of relief even in those cases in which surgical procedures are inadvisable. It is of the utmost importance to bear in mind, however, that the inoperable cases submitted to radium fall into two categories: (1) Those in which it seems best to make a strong effort to bring about a clinical recovery. (2) Those in which only palliative treatment is advisable. Failure to recognize the latter class of cases will result in disappointment and even may cause great harm. Indeed, it is better to omit treatment altogether rather than to attempt the impossible and cause additional suffering from radium effects.

The whole principle of the disappearance of carcinoma or other malignant growths under the influence of radium rays is based on the fact that the tumor cells are more susceptible to the rays than the normal tissues. According to many different authors, certain types of carcinoma cells are four to seven times as sensitive as most normal cells. According to Friedrich and Kroenig's experiments with x-rays, the radiosensitiveness of breast carcinoma to the middle epidermal cellular layer is in the ratio of 170 to 150, i.e., 1.15 to 1. In other words, a dose of x-rays that will not destroy the epidermis will cause the resolution of breast carcinoma. Certain cases of squamous cell carcinoma are probably only

slightly more radiosensitive than the middle epidermal layer. Radiation that falls short of destroying normal tissues will often cause necrosis and disappearance of the tumor itself. One strives, therefore, to produce with radium a change in the growth that will not at the same time be accompanied by serious injury to the healthy tissue. This is best accomplished by giving maximum doses at the outset. Subsequent doses should always be of less intensity.

Some authors believe that a single intensive dose is best in dealing with malignant growths. This procedure seems to me, however, to be practical in only a few cases and sometimes is not without danger to the patient. Ordinarily, several intensive doses at suitable intervals are in my opinion to be preferred.

In many inoperable cases that come under radium treatment, metastasis has already taken place. In such cases, palliation is all that can ordinarily be hoped for, although the primary growth can occasionally be healed by radium.

We may now refer to the radium treatment of malignant disease occurring in different situations in the body.

THE TREATMENT OF CARCINOMATA

For convenience of description we may group together carcinomata affecting the different organs.

1. Epithelioma of the Skin

The problem of treatment of epithelioma of the skin depends to a great extent upon the type of growth that is present.

(a) Squamous-cell Epithelioma

If the case is considered operable by the surgeon and the adjacent glands are palpable, the draining lymphatic glands and growth may be excised "en bloc." If the glands are not palpable, operation may be limited to the growth and radiation given to the glands. There is little doubt, however, that even in distinctly operable cases, preoperative radium treatment will be of advantage. At the time of operation, emanation ampoules may be buried in the operation field. After operation, prophylactic radiations should also be given. Over dosage should be guarded against. With an early diagnosis, recovery should be brought about in at least 95 per cent of the cases.

Inoperable cases of squamous-cell epithelioma may frequently be retarded in their progress for considerable periods of time and in some instances a clinical recovery may be brought about. The diagnosis of squamous-cell from basal-cell epithelioma is frequently impossible without a microscopic section and as it is often inadvisable to obtain this a

few of the clinical points of difference may be indicated. (1) Its location. Epitheliomas of the lower lip, tongue, penis and extremities are usually of the squamous-cell type. One-half of the epitheliomas of the upper lip are also of this type. (2) A papillomatous aspect to the growth is indicative usually of squamous-cell cancer. (3) Rapidly growing epitheliomata with metastases to the adjacent lymphatic glands are practically always of the squamous-cell type.

It must be emphasized, however, that there is no absolute rule holding in all cases that allows of a complete clinical differentiation.

The technic of the radium treatment of squamous-cell epithelioma of the glabrous skin when it is for any reason inoperable naturally varies with the clinical type.

For very small and superficial growths "one quarter" or "one half strength" glazed plaques may be used. Screened with 0.1 mm. of lead and applied in direct contact with the skin, a total exposure of six or more hours may be given in several periods of one to two hours each.

In dealing with larger, deeply infiltrated and ulcerated growths, it is best to use only gamma rays. In some cases two hundred millicuries, screened with two millimeters of brass and arranged so that it is concentrated in the proportion of 5 millicuries per square centimeter may be applied at a distance of 3 centimeters for thirty hours in periods of ten or more hours each. In six weeks, if there are evidences of the disease persisting, a similar course but of less intensity should be given provided signs of radium reaction are absent. Great care should be taken to avoid "burns" which may be very painful and prevent further treatment at a critical time. Some advise vigorous treatment with unscreened applicators for certain refractory types and even in ordinary cases. This procedure, however, causes considerable inflammatory reaction and if unsuccessful precludes for a time further treatment in most cases on account of the pain. We prefer, therefore, the former method in ordinary cases but in some cases we resort to the unscreened glazed applicators. In some cases bare emanation ampoules may be buried in the growth. For the prophylactic treatment of the adjacent lymphatic glands powerful deep radiations are advisable. Four hundred millicuries (5 mc. per square cm., 2 mm. screen, 6 cm. distance) may be applied for a total of thirty hours.

(b) **Basal-cell Epitheliomata**

In the treatment of basal-cell epitheliomata, radium, in our judgment is the most satisfactory agent we possess and sometimes succeeds when everything else fails. In spite of some statements to the contrary, we believe that this type of epithelioma is one of the most amenable of all types of new growth to radium. Failure may, of course, occur in very extensive cases in which the loss of tissue is very great and repair is

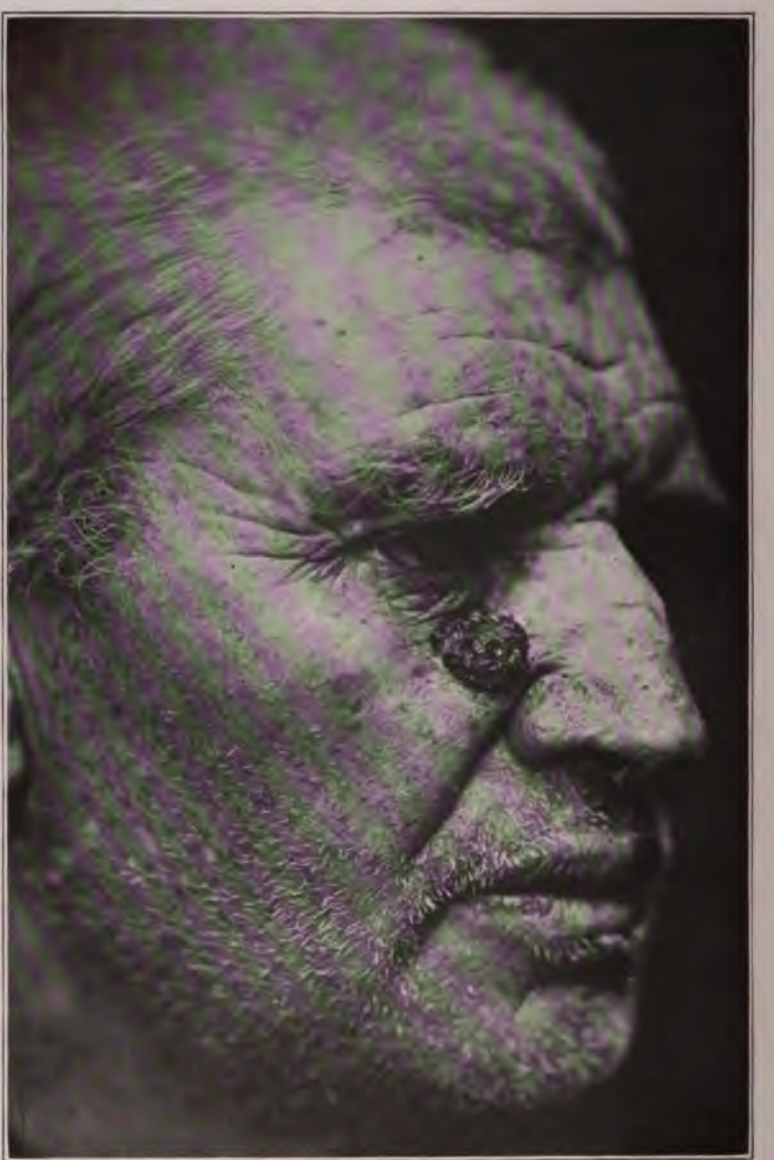


Fig. 38.—Epithelioma of right cheek.

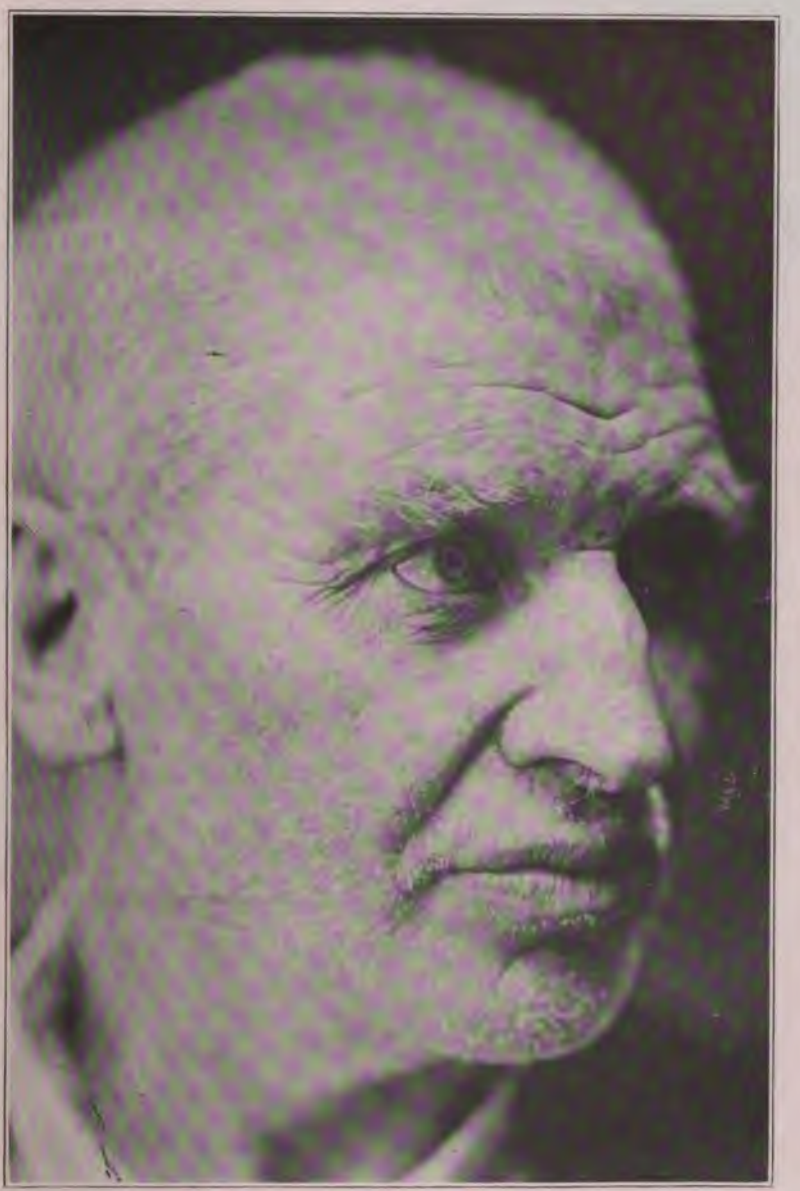


Fig. 39.—Patient in Fig. 38 after radium treatment.

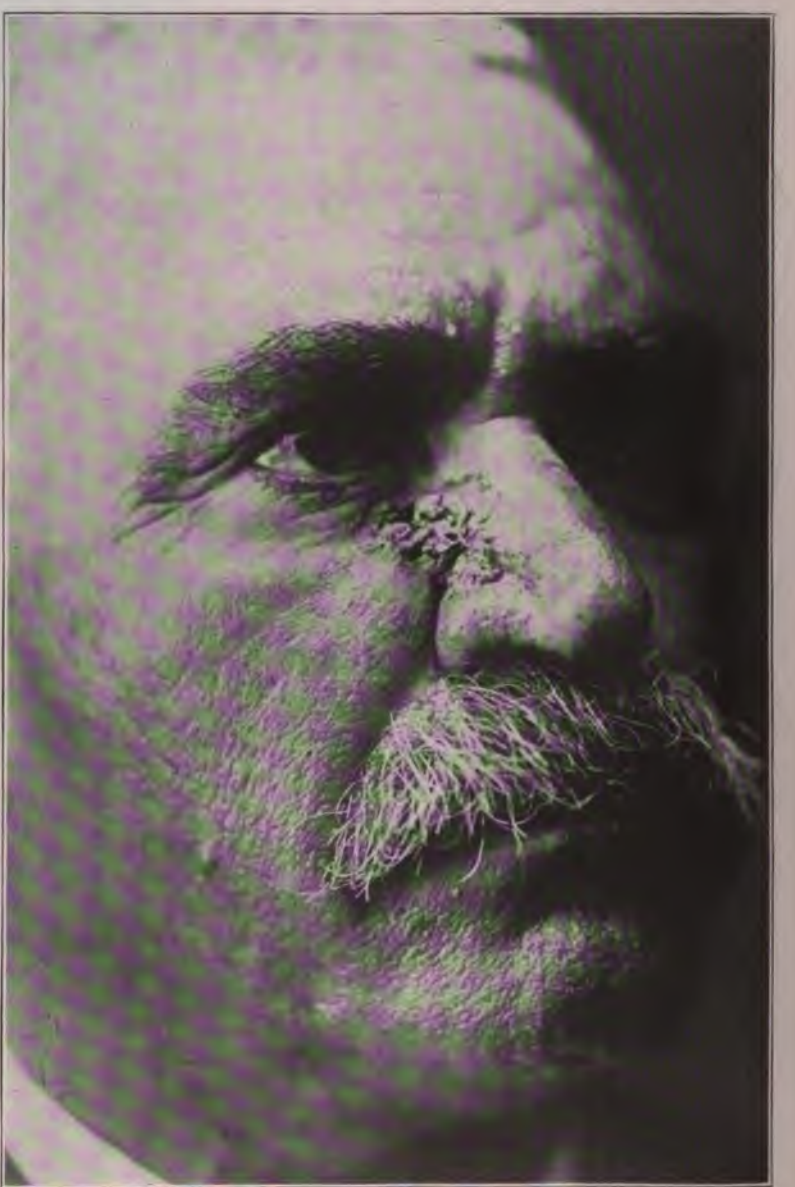


Fig. 40.—Epithelioma of right side of nose.

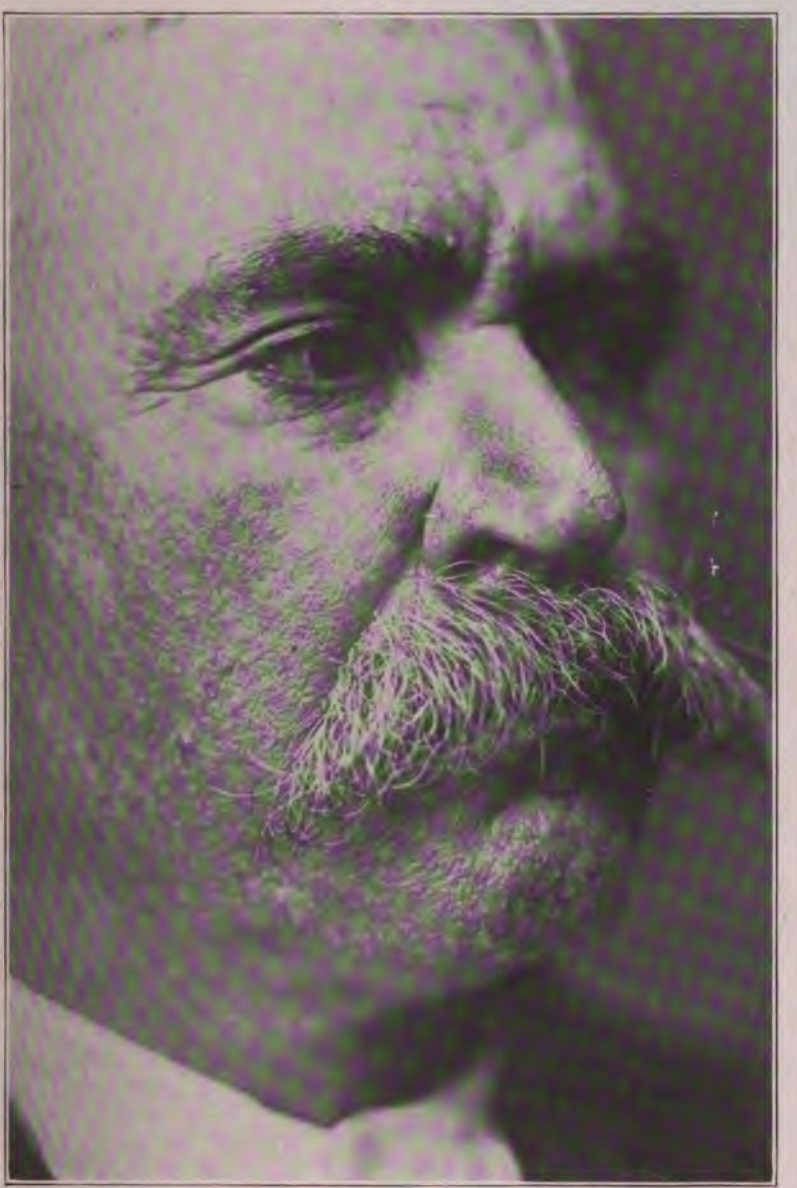


Fig. 41.—Patient in Fig. 40 after radium treatment.

Fig. 42.—Epithelioma of tip of nose.

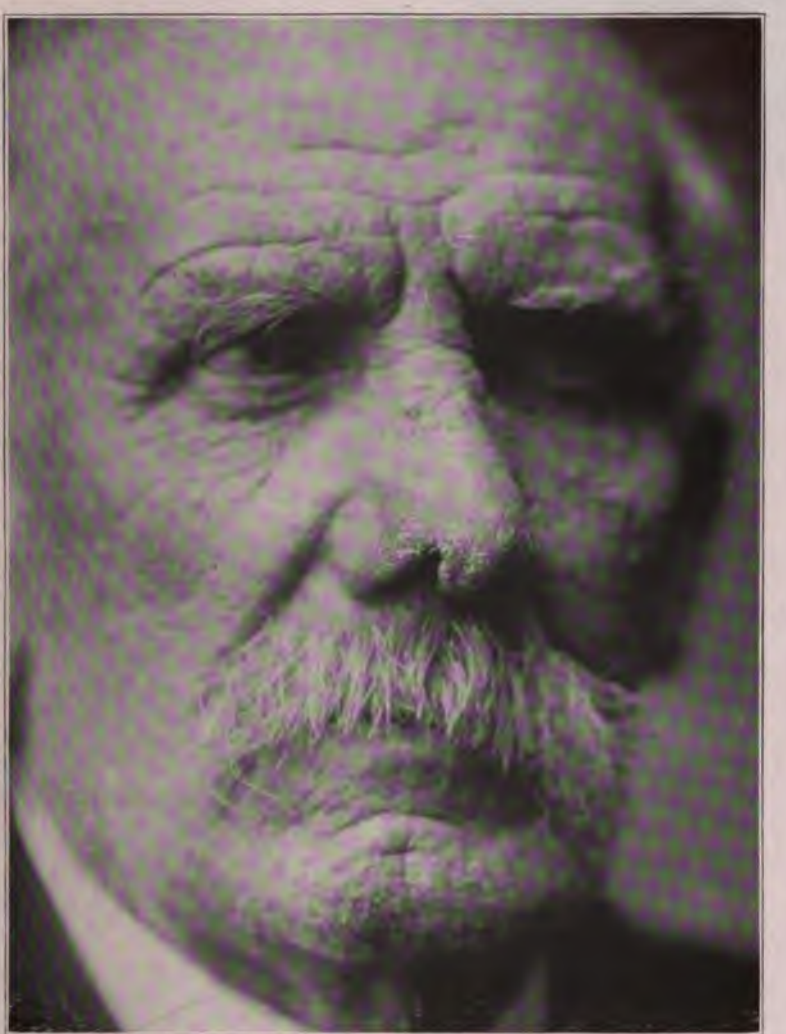


Fig. 43.—Patient in Fig. 42 after radium treatment.

Fig. 44.—Epithelioma of left lower eyelid.

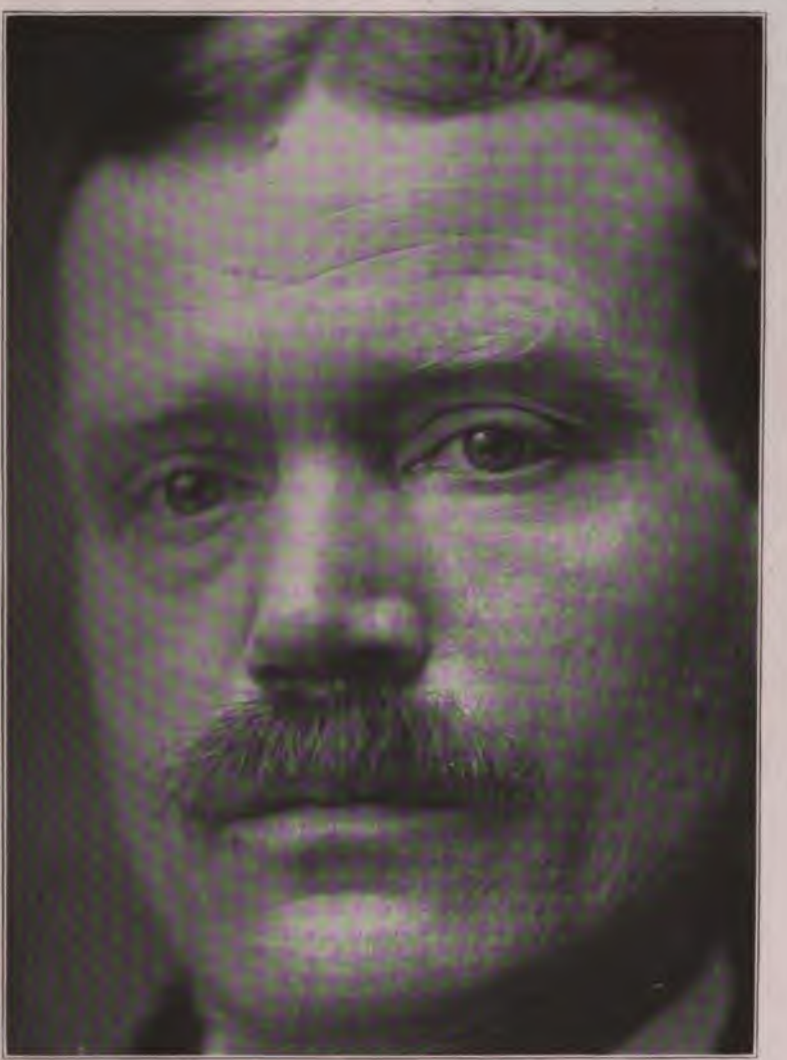


Fig. 45.—Patient in Fig. 44 after radium treatment.

Fig. 46.—Epithelioma of right inner canthus, eyelids and nose.

Fig. 47.—Patient in Fig. 46 after radium treatment.

Fig. 48.—Epithelioma of left inner canthus, eyelids, nose, cheek and upper lip.

Fig. 49.—Patient in Fig. 48 after radium treatment.

Fig. 50.—Epithelioma of the right temple.

Fig. 51.—Patient in Fig. 50, after radium treatment.

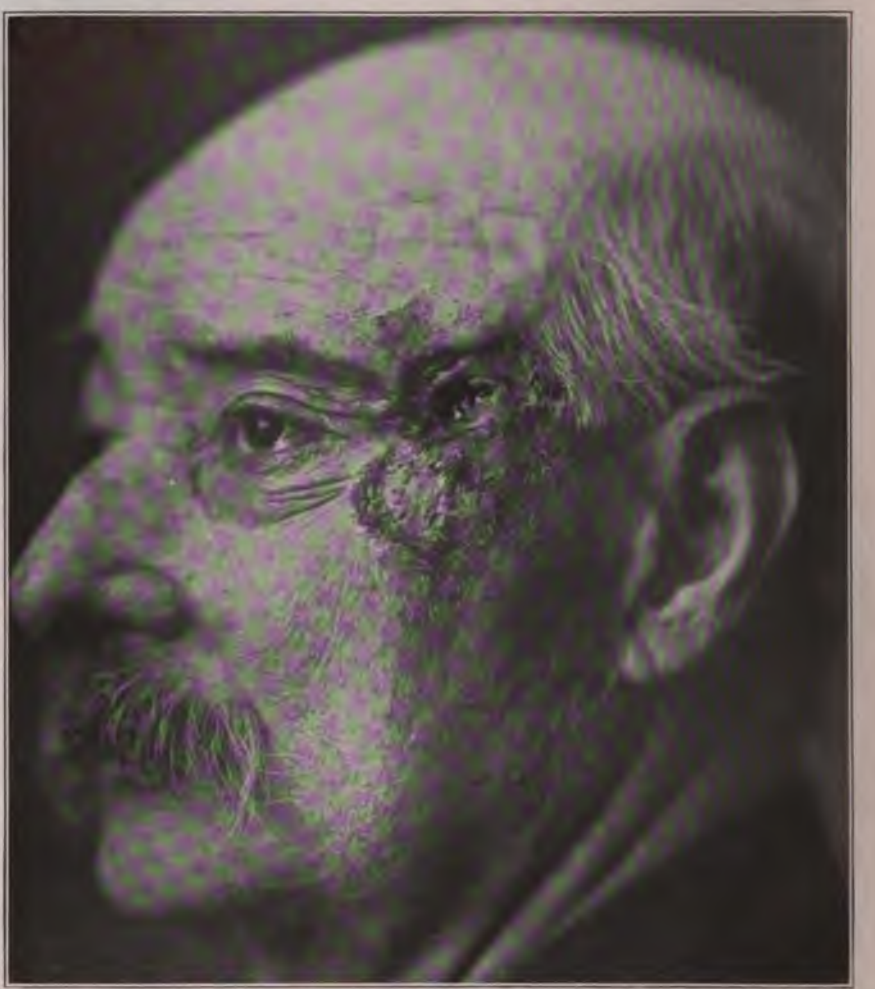


Fig. 52.—Epithelioma of the left temple.

Fig. 53.—Patient in Fig. 52 after radium treatment.

Fig. 54.—Epithelioma of left malar region. Patient referred by Dr. Joseph Scheurich.

Fig. 55.—Patient in Fig. 54 after radium treatment.

Fig. 56.—Epithelioma of forehead.

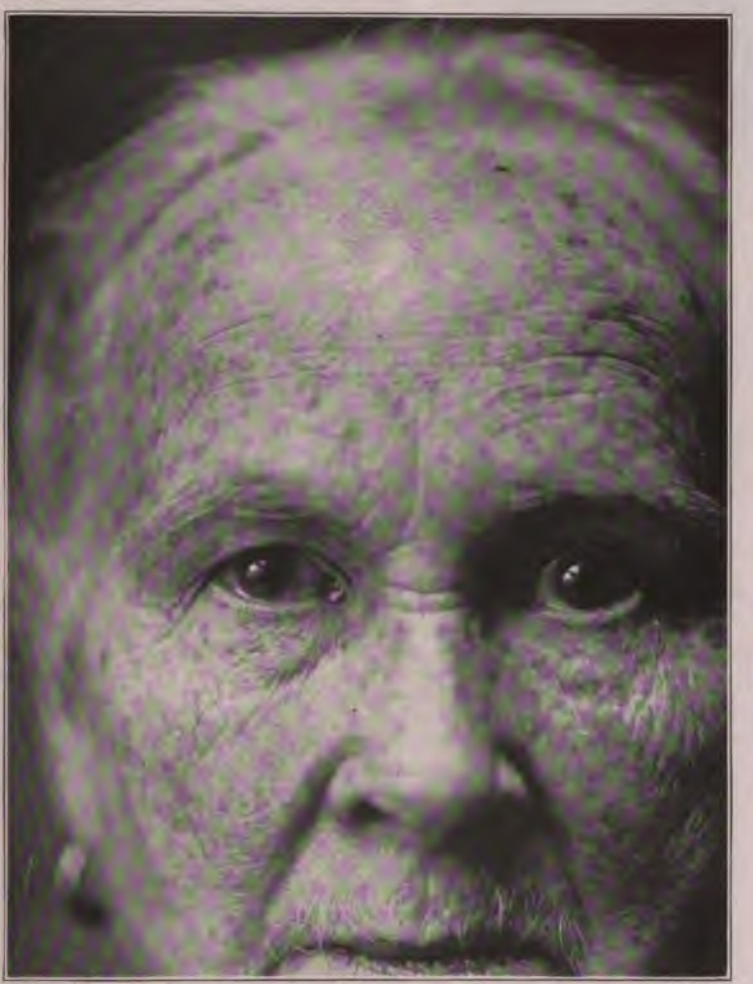


Fig. 57.—Patient in Fig. 56 after radium treatment.

Fig. 58.—Epithelioma of right ear.

Fig. 59.—Patient in Fig. 58 after radium treatment.

Epithelioma situated below right ear of 3 years' standing.

Fig. 61.—Patient in Fig. 60 after radium treatment.

Fig. 63.—Patient in Fig. 62 after radium treatment.

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Epithelioma of the Nasal Mucosa

...ay be treated by carrying the radium
...e through the anterior nares into the
... may be employed for sarcoma and
...nose and nasopharynx. One hundred
...s, arranged end to end, screened with
...r two millimeters of rubber may be
...each for a total exposure of 6 hours.
...poules may be successfully buried

Epithelioma of the Lip

...arises about one half of the cases of
...ently at the junction of the mucous
...gin, however, on the cutaneous
...usually of the squamous-celled type.

Speaking very generally if the lesion is less than a centimeter in diameter and is not deeply infiltrated, radium may be used alone with expectation of success in selected cases. Larger lesions should be treated by preoperative radiation and excision. Postoperative radiation is always advisable.

In the application of radium to the growth, the usual technic consists in the use of not less than 200 to 300 mc. This may be screened with 1 mm. of silver plus 2 mm. of rubber. One should radiate an area extending several centimeters beyond the visible disease. Certain tumors should be attacked from the superior, the internal and the external aspect of the lip. Six hundred mc. hours may be given to an area of 4 square centimeters. This technic produces sharp reaction.

If the adjacent lymphatic glands are not palpably enlarged, they may be left undisturbed by the surgeon but should receive heavy prophylactic gamma-ray radiation. If the adjacent glands are palpably enlarged, conservative surgical removal may be undertaken in selected cases. The operation may be preceded and followed by surface radiation. In some cases bare emanation ampoules may be buried in the operative field following removal of the lymphatic structures or in the glandular masses in case they are not removed but merely surgically exposed.

(4) Carcinoma of the Lingual, Buccal and Pharyngeal Mucous Membranes

While epithelioma of these structures is frequently refractory to radium, very good and even brilliant results may sometimes be obtained. The most notable advance in the treatment of cancer in these situations consists in the use of bare emanation ampoules which are inserted into the tumor in the manner previously described and allowed to decay *in situ*. When surface applications are made, we would advise the use of not less than 200 millicuries. The radium should be screened with 1 millimeter of silver and 2 millimeters of rubber. An exposure of five hours in divided doses may be given. For holding the radium in position we frequently utilize the dental composition material suggested by Janeway.

At the present time, in suitable cases, we invariably bury bare emanation ampoules in growths of the accessible mucous membranes.

Leukoplakia

It must be remembered that patches of leukoplakia may disappear spontaneously if tobacco is discontinued.

The radium treatment of leukoplakia, which is such a frequent precursor of epithelioma of the lingual, buccal and pharyngeal mucous membranes, is often successful. A caustic dose must often be employed in order to bring about the desired result, but at times deeper and less caustic radiations may be given. A method that we have frequently

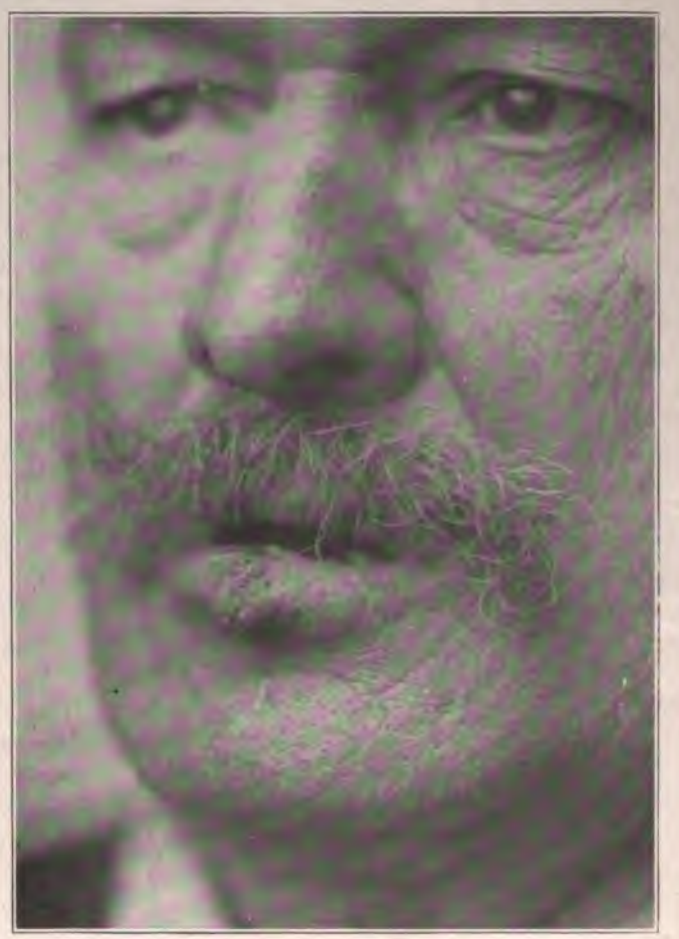

Fig. 64.—Epithelioma of lower lip.

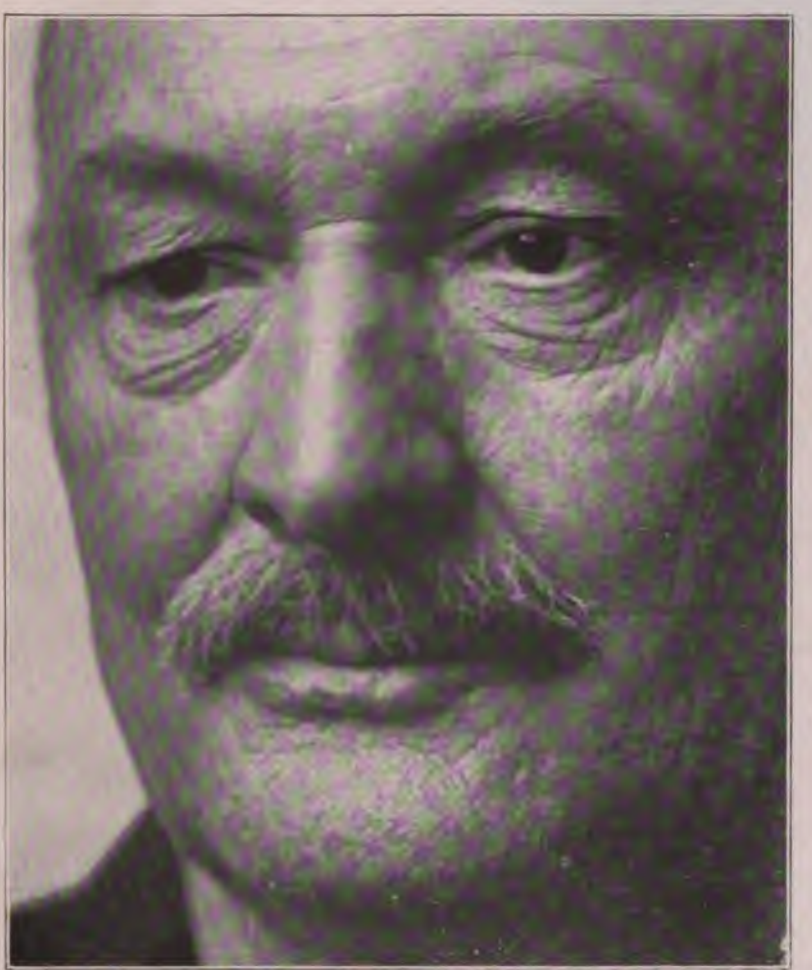

Fig. 65.—Patient in Fig. 64 after radium treatment.

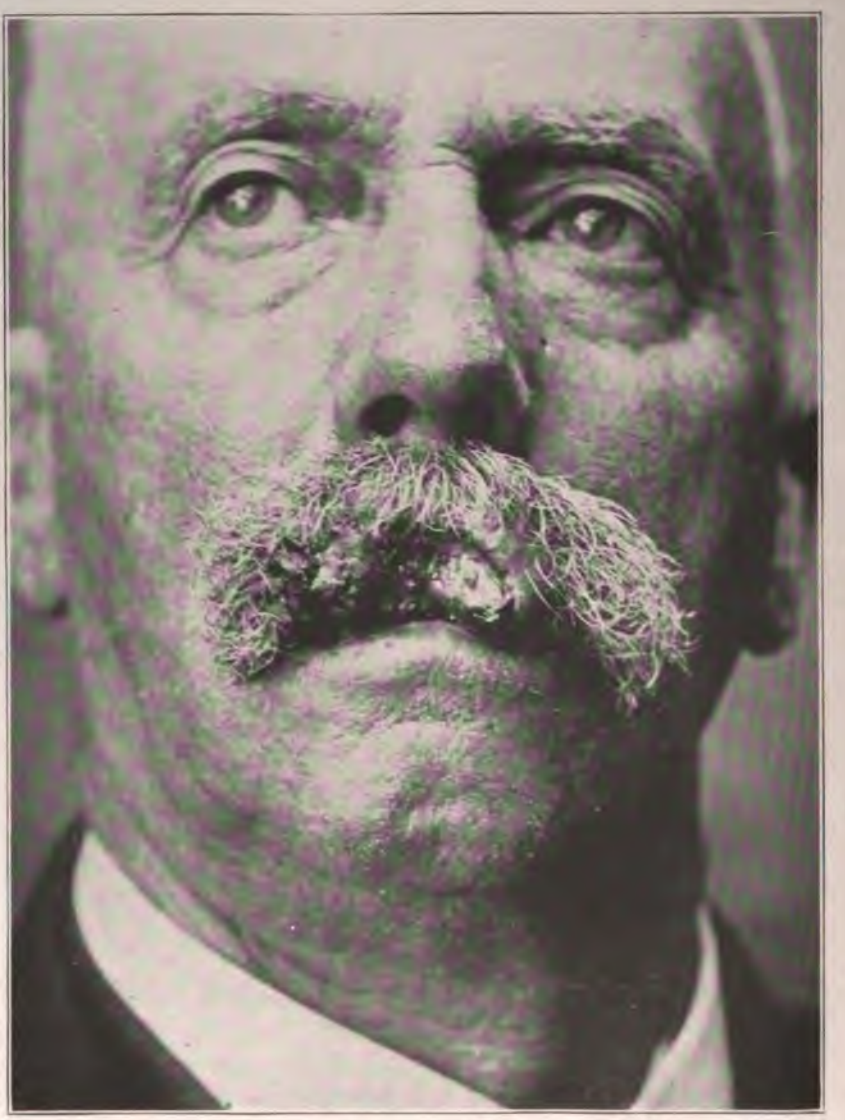

Fig. 66.—Epithelioma of upper lip.

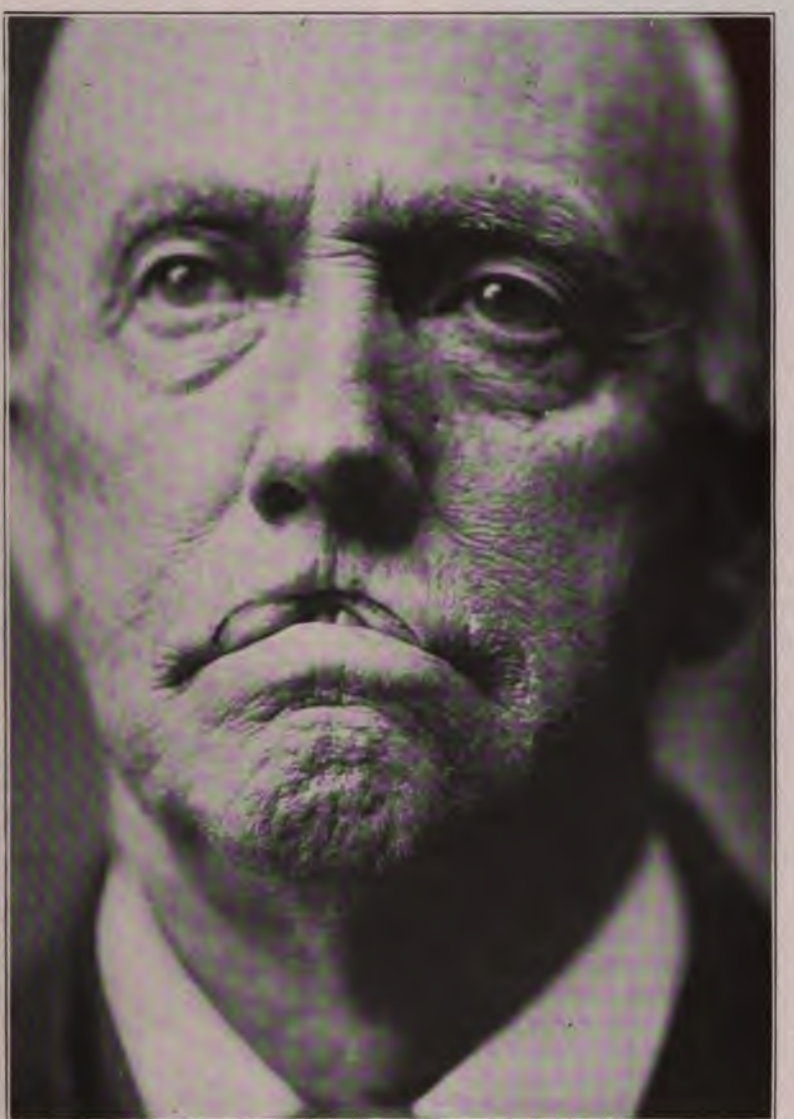

Fig. 67.—Patient in Fig. 66 after radium treatment. The insertion of false teeth gives the mouth a distorted appearance.

Fig. 68.—Epithelioma supervening on leukoplakia of right cheek.

Fig. 69.—Patient in Fig. 68 after radium treatment.

Fig. 70.—Carcinoma of the tongue in patient aged 65 years. Patient referred by Dr. E. P. Berg. Photograph taken July 7, 1921.

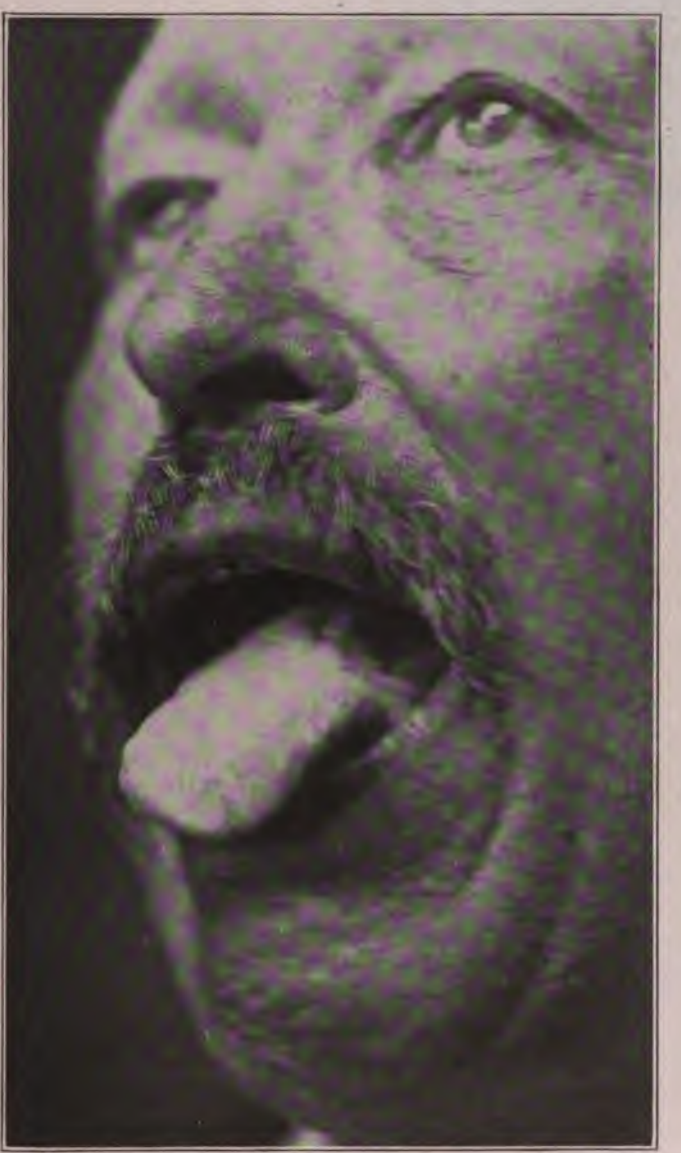

Fig. 71.—Patient in previous figure after insertion of 19 millicuries of radium emanation contained in 15 bare glass ampoules. Photograph taken July 15, 1921. Six months later patient appeared clinically well.

used consists in the application of 80 millicuries concentrated in the ratio of 10 millicuries per square centimeter. This may be screened with 1 millimeter of silver and 2 millimeters of rubber. A total exposure of eight hours in periods of one or two hours each may be given.

We may now refer particularly to carcinoma of the tongue and carcinoma of the tonsil.

(a) Carcinoma of the Tongue

Cancer of this structure is always of the squamous-cell type. It is the most likely of all cancers to invade the lymphatic glands early and widely. This in itself precludes successful treatment in many cases. In the most extensive cases, palliation only can be hoped for. Sometimes cases seem to yield quite satisfactorily to the insertion of radium, contained in metal needles, into the growth. I have reported a case treated in 1917 in this manner, who is well at the time of writing. In this case, 60 milligrams were inserted into the growth for thirteen and one-half hours, and seven weeks later 72 milligrams for twelve hours. Hayward Pinch has buried approximately 21 to 53 millicuries, contained in a platinum needle, in certain nodules for twenty-four hours. Sharp reaction follows this treatment and in some cases the nodule becomes replaced with scar tissue. The method of using bare emanation ampoules has practically replaced the use of metal needles. In some cases, surface applications may be advantageously combined with the method of burying bare glass emanation ampoules. The greatest care must be used not to give an overdose and produce sloughing. It must not be forgotten also that healing can only occur when a bed of healthy tissue capable of producing good granulations surrounds the growth. The regional lymph nodes may be treated in the manner already described.

(b) Carcinoma of the Tonsil

Cancer in this situation frequently yields to radium and sometimes displays a marked susceptibility. If metastases from a tonsillar growth are present in the neck these growths are also more than ordinarily sensitive to the rays. If the growth has extended to the tongue, the prognosis becomes the same as for cancer of that organ.

We have successfully treated numerous cases of cancer of the tonsil. While formerly metal needles containing the radium were inserted in the growth, these have practically been given up in favor of the bare glass ampoules containing radium emanation. Radium may be applied to the surface of the tonsil by means of a wire holding a specially constructed piece of dental modelling compound adjusted to the area to be treated. Two hundred millicuries screened with the equivalent of 2 millimeters of brass and 2 millimeters of rubber may be applied for three hours in periods of one hour each. The intensity of the treatment to be

given naturally depends upon the extent of the disease. If the growth projects several millimeters above the level of the normal mucous membrane, larger doses will be tolerated as the tumor tissue acts as a filter and in addition, the distance of the radium from the normal tissue is obviously increased. Instead of surface applications, several bare emanation ampoules may be buried in the growth. Five-tenths to 1 mc. or more of emanation to each cubic centimeter of tissue may be used. In suitable cases, the combination of these two methods seems to be superior to either method used alone. Overdosage must be carefully avoided.

(5) Carcinoma of the Superior Maxilla

Many cases respond favorably to radium treatment. The disease most often begins at the alveolar process of the jaw. Carious teeth are usually found in these cases and the disease may apparently have started around one of them. The antrum is usually invaded early by the growth. Metastasis occurs relatively late in the disease. In the application of radium, the antrum, if involved, should be opened, usually above the alveolar process. Indeed in any case it is not wise to allow the antrum cavity to remain closed. By means of long silver wires carrying the tubes, the radium may be brought into direct contact with the growth. In addition, heavy treatment may be given externally over the cheek and within the cavity of the mouth so as to radiate the growth from all sides. In the technic of treatment, much depends upon the situation and extent of the disease. Within the cavity of the antrum, 200 millicuries screened with 2 mm. of brass and 2 mm. of rubber may be applied for five hours. In the mouth, 200 mc. with the same screening may be used for five hours. Externally, 250 mc., screened with 2 mm. of brass and arranged on a pad covering 50 sq. cm., may be used for thirty-six hours at a distance of three centimeters in several periods of six to twelve hours each. G. B. New of the Mayo Clinic has used a combination of heat and radium in cancer of the jaw and cheeks. In cancer involving the antrum a soldering iron at a dull heat is carried into the antrum cavity and the growth is burned away. About two weeks later, when the slough has come away, radium is introduced into the antrum cavity.

(6) Carcinoma of the Inferior Maxilla and Floor of the Mouth

Cancer of the lower jaw usually begins on the alveolar process. Sooner or later, the floor of the mouth is involved and indeed it is frequently impossible to determine in just what structure the growth originated. In some cases, the floor of the mouth is the primary seat of the disease. As a rule, metastatic involvement of the lymphatic glands of the neck occurs early. On this account cancer of the floor of the mouth is much more malignant than cancer of the superior maxilla or cancer of the

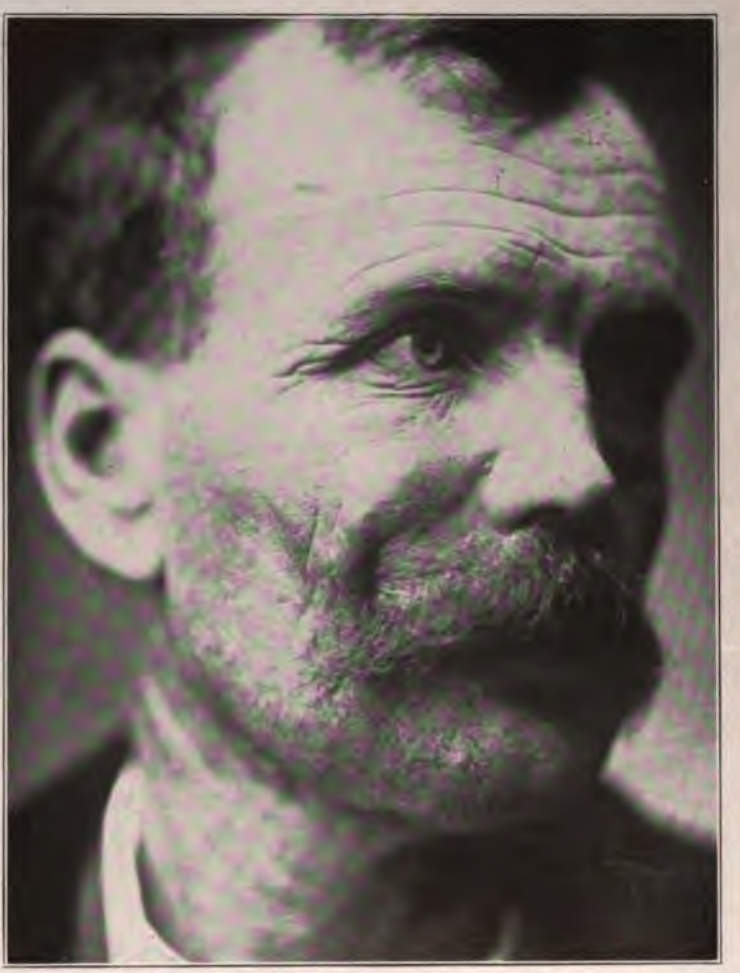

Fig. 72.—Carcinoma of right superior maxilla involving antrum. Photograph taken January, 1915.

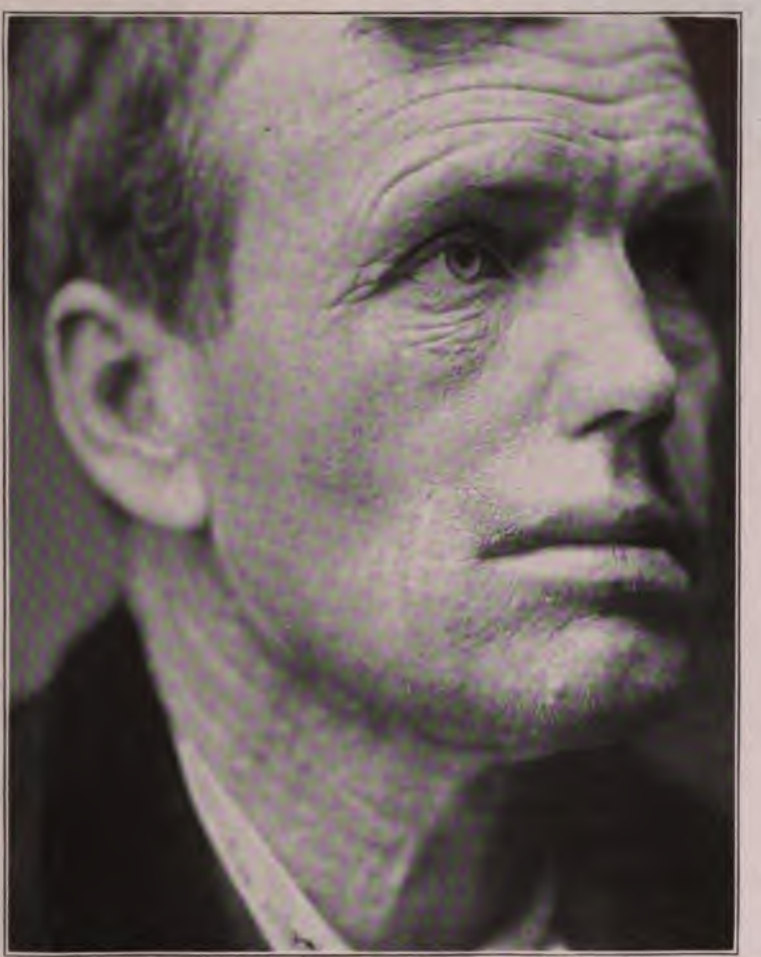

Fig. 73.—Patient in Fig. 72 after radium treatment. Photograph taken April, 1915.

buccal mucous membrane. When metastases to the neck are absent, radium treatment frequently produces a clinical retrogression and even complete healing of the growth. If the lymphatic glands of the neck are involved, retardation of the disease is all that can ordinarily be hoped for, although the primary growth may disappear under treatment. Two hundred millicuries screened with 1 millimeter of silver and 2 millimeters of rubber may be applied to the surface. A total exposure of four or more hours may be given. Instead of surface applications, several bare ampoules may then be buried in the lesion; 0.5 mc. to 1 mc. per cubic centimeter of tumor tissue may be used. The different areas of the neck likely to harbor metastases may receive prophylactic exposures. Five hundred millicuries screened with two millimeters of brass or its equivalent and concentrated on an applicator that has a superficial surface of 50 square centimeters may be used at a distance of 6 centimeters. A total exposure of twenty-five hours may be given in periods of ten or more hours each. If metastases are present, retardation of the growth may be brought about by the ordinary treatment for carcinomatous glands.

(7) Carcinoma of Cervical Glands; Carcinoma of Thyroid Gland; Parotid Tumors

For clinical convenience, carcinoma of the lymphatic glands of the neck, carcinoma of the thyroid gland, and tumors of the parotid gland may be considered together.

(a) Carcinoma of the Cervical Lymphatic Glands

These cases are usually secondary to carcinoma elsewhere. The primary focus is most frequently in the labial, buccal, pharyngeal, lingual or laryngeal mucous membrane. The supraclavicular glands are frequently involved in mammary cancer. The primary focus from which carcinoma of the lymph nodes originates may even escape detection altogether. In most of the mouth cases, the neighboring lymphatic glands sooner or later become involved although this event may be delayed for a considerable time. The treatment may be carried out by surface applications, by burying metal needles containing radium or radium [illegible], or by burying bare emanation ampoules. Sometimes a combination of these methods is most desirable. Isolated and movable glands [illegible] removed surgically prior to radium treatment. Following operation [illegible] needles of radium emanation may be inserted in the operative [illegible]. If surface applications are used, 500 millicuries may be applied at a [illegible] centimeters. Concentrated in the ratio of 5 to 10 millicuries [illegible] and screened with the equivalent of 2 millimeters [illegible] twenty-five hours in several periods of ten or [illegible] given. If metal needles are inserted, 5 to 75

millicuries in steel needles that have a wall thickness of 0.4 mm. may be buried for twelve or eight hours. If bare emanation ampoules are buried in inoperable masses, a dose of 0.5 to 1 mc. or more per cubic centimeter of tumor tissue may be given. Considerable judgment must be exercised in treating carcinomatous lymph glands. It must be remembered that the usual effect is retardation of the growth and that curative results can seldom be hoped for. Individual masses of glands that have some degree of mobility and are not too large may sometimes be removed by radium. Masses of glands that are fixed, poorly nourished and of large extent can seldom be successfully treated. Doses powerful enough to cause death of the cancer cells may produce under these conditions sloughing of large areas of normal tissue, which may add to the patient's discomfort and hasten his end.

Douglas Quick has recently described the procedure used at the present time at the Memorial Hospital, New York, in dealing with cervical lymph nodes associated with intraoral cancer.

In cases with no palpable nodes, surface radiations over the neck are employed, but excision of the lymphatic structures is not undertaken.

In cases with palpable and operable nodes, surface radiations are followed by a neck dissection, preferably under local anesthesia. Following removal of the lymphatic structures, 5 to 15 mc. of radium emanation in bare glass ampoules are embedded in the operative field. Following this procedure, surface radiations may be used on the opposite side of the neck. Too much radiation over the affected side may devitalize the tissues. If it is found that the disease, at the time of operation, has perforated the gland capsule, radical surgical removal is deemed unwise and the mass is infiltrated with bare emanation ampoules, the wound being then closed. The statistics of this author are encouraging.

(b) Carcinoma of the Thyroid Gland

Some cases of this disease are strikingly benefited. The technic of treatment should be wholly by external or surface radiations. Burying emanation needles in these tumors may result in an intractable fungating growth. Powerful deep radiations must be used. Six hundred millicuries screened with the equivalent of 2 millimeters of brass and in the ratio of 5 to 10 millicuries per square centimeter may be applied at a distance of 6 centimeters. A total exposure of twenty hours in periods of ten or more hours each may be given. Metastasis to the bones or other organs may take place several years after apparent recovery.

(c) Parotid Tumors

In carcinoma, endothelioma, and certain mixed parotid tumors, encouraging results have been obtained. In tumors containing cartilage not so much effect is to be anticipated. The technic may consist of the

application of 250 millicuries at a distance of 3 centimeters. Concentrated in the ratio of 2.5 millicuries per square centimeter and screened with the equivalent of 2 millimeters of brass, a total exposure of thirty hours divided into periods of ten or fifteen hours each may be given. As in all other tumors, the technic varies with the apparent depth of the growth and the area that it covers.

It is not advisable to introduce radium or emanation needles into the parotid gland. Hayward Pinch has called attention to the ill effects that are likely to follow this procedure. A severe reaction following the introduction of an emanation needle may result in the formation of a sinus which is kept open by the parotid secretion and from which an intractable ulceration may start.

(8) Carcinoma of the Larynx

In carcinoma of the upper larynx, or so-called extrinsic carcinoma, the results have been encouraging. In selected cases, one of the most effective methods of radium application consists in the introduction of steel radium needles, each containing twelve milligrams of element or millicuries of emanation directly into the growth. The needle introducer devised by Dr. O. T. Freer is valuable for this procedure. The needles may be left in the tissues for from eight to twelve hours. In one case of carcinoma of the epiglottis, base of the tongue and left vallecula, treated by the writer in conjunction with Dr. Freer, complete recovery occurred. In this instance there has been no local recurrence for over four years, but a recurrence in the glands of the neck two years ago yielded to radium. The patient is now clinically well. This case has been previously reported by the writer.

In intrinsic carcinoma of the larynx, radiation from the outside or inside of the larynx may be employed. Kelly and Burnam have referred to several cases treated by external radiations that have recovered and remained well for varying periods. Ordinarily, however, the combination of internal and external treatment is necessary for success. It is doubtful whether external radiations alone are sufficient to cause complete regression. G. B. New of the Mayo Clinic has treated intrinsic carcinoma of the larynx in the following manner: "Tracheotomy is first performed and after cocainization the radium is dropped directly into the larynx. The radium is held in place for from one to one and one-half hours at a time. While all patients are not benefited, very encouraging results and remarkable relief have been obtained. One man had an extensive carcinoma of the larynx obstructing the glottis so that it was necessary to do a tracheotomy; he was swallowing fluids only. In two months time he had gained forty-eight pounds in weight and could eat anything. He had a cork in the tracheotomy tube. The growth did not recur

locally but the patient died of chest metastases about fourteen months later. However, the treatment gave him a year of comfort."

A method that promises to be even more effective than the one just described because it allows of accurate localization, consists in the application of the radium to the interior of the larynx by means of the special apparatus devised by Dr. O. T. Freer. This apparatus is described in the chapter devoted to a consideration of the use of radium in laryngology. Screened with 1 millimeter of silver, 200 millicuries contained in 4 or 5 tubes may be used, in periods of twenty or more minutes each for two hours. During intralaryngeal treatments the throat must be kept free of saliva by an electric suction pump.

(9) Carcinoma of the Esophagus

In this all but hopeless disease the results of radium treatment in a number of cases have been encouraging. Among those who have reported their results, some of which have been favorable, are Abbe, Exner, Einhorn, Finzi, Hayward Pinch, Janeway, Mills and Kimbrough and the writer. Abbe reported a case alive and well nine years after treatment. Mills and Kimbrough have seen favorable results. In the cases reported by the two last-named authors, the coincident use of the x-rays enabled them to localize more accurately the position of the bougie carrying the radium in the esophagus. In one case, Finzi obtained a clinical recovery that had been maintained for three years when the case was reported. In another case a clinical recovery was maintained for four years when the patient died suddenly. Postmortem there was found carcinomatous involvement of a small intercostal branch of the aorta with resulting hemorrhage.

In one of the writer's cases, treated in conjunction with Dr. John A. Cavanaugh, apparent recovery was maintained for about one year when the patient died suddenly of cerebral hemorrhage.

Technic of Treatment of Carcinoma of Esophagus.—Previous to undertaking treatment, careful localization of the growth is all important. Skiagraphs with and without a bismuth meal, direct esophagoscopy and measurements with bougies usually afford sufficient information. It is necessary that the lumen of the growth admit a bougie several millimeters in diameter in order that the properly screened radium may pass completely within the stricture. In some cases, several days prior to the treatment, a silk thread may be swallowed by the patient. The bougie holding the radium may then be threaded upon the silk thread. This procedure will sometimes enable one in difficult cases to engage the apparatus in the lumen of the growth. The treatment may consist of the application of 100 to 150 mc., screened with 1.5 mm. of silver. The bougie containing the radium emanation is passed into the strictured part of the esophagus and maintained in position for about eight hours. Prior

to the treatment morphine and atropine may be given hypodermically. A special attendant should maintain the bougie in place. Several treatments may be given at intervals of 3 or 4 days until the patient has received about 1500 mc. hours.

Another technic adapted to certain cases and suggested by Janeway consists in the following procedure. A preliminary gastrostomy is performed. A silk thread is subsequently swallowed by the patient and the lower end is pulled out through the gastrostomy wound. A series of several radium tubes is then attached to the oral end of the string and pulled through the stenosed tract by means of the lower end. The upper tube is of such size that it will not slip through the strictured part of the esophagus but will rest upon the upper end of the carcinoma. Janeway has used several tubes, containing 30 or 35 mc. each, for from four to six hours.

The immediate results of treatment are an improvement in swallowing due perhaps to the mechanical dilatation. About ten days later there may be increased dysphagia due to the onset of reaction. The hemorrhage, odor and purulent discharge that may attend the passage and withdrawal of a bougie prior to treatment are no longer present. In a few weeks, as the reaction from the radium subsides, dysphagia is relieved and the patient may be able to swallow all kinds of food for a number of months. Greatly increased body weight and improvement in the general condition are usual accompaniments of the increased power of swallowing.

(10) Carcinoma of the Stomach and Intestines

In inoperable or recurrent carcinoma of the stomach and intestines it is permissible to use radium in the hope of retarding the disease and relieving pain. Janeway has seen improvement follow a combination of posterior gastroenterostomy and radium treatment. After the above operation was performed, several radium tubes were pulled into place through the gastrostomy wound by means of a string previously swallowed. We have used a similar method for carcinoma of the sigmoid flexure of the colon. Inguinal colostomy was first performed. By means of a string passed through the distal portion of the bowel from the opening in the colon to the anus a string of tubes was pulled backward through the anus until they engaged within the lumen of the affected portion.

Technic of Treatment of Carcinoma of Stomach and Intestine. Palliation is all that can be hoped for in these conditions. Symptomatic improvement has been noted following powerful, deep treatment to the abdominal wall. The condition demands the use of at least 500 mc. This should be screened with 2 mm. of brass and placed at a distance of 6 to 10 cm. The concentration may be in the ratio of 5 mc. per square centi-

meter. At a distance of 6 cm. an exposure of twenty-five hours and at a distance of 10 cm. an exposure of thirty-six hours may be given in periods of ten or more hours each.

(11) Carcinoma of the Rectum

Considerable experience has been accumulated in the radium treatment of this disease. Rectal carcinoma varies a good deal in its response to radium. Adenocarcinoma of the annular, vascular type, situated in the upper half of the rectum, is probably more amenable than growths occupying only a portion of the rectal lumen and deeply infiltrating the rectal wall. Epidermoid carcinoma in close proximity to the anal region is less easily influenced than the other types. A number of cases of complete regression of the growth and apparent clinical cure persisting for varying periods of time have been reported by different authors. The percentage of clinical recoveries is not over 10 per cent. It must be remembered, however, that as a rule only cases in which surgical intervention is impossible are treated. Fully one-third of the cases are distinctly improved. In borderline cases, radium treatment may render operation possible.

Technic of Treatment of Carcinoma of the Rectum.—The method of treatment and the dosage vary. Applications to the surface of the carcinoma may be made by introducing the tubes attached to a long silver wire into the rectum. In other cases, bare emanation ampoules may be buried in the growth. These methods may also be combined.

Carcinoma involving a segment of the rectal wall is best adapted to the use of buried emanation ampoules. Carcinoma of the annular type may be treated by surface applications alone. In either condition, however, the combined methods may be used.

If tubes are inserted into the rectum they may ordinarily be applied by means of a long pliable silver wire which is bent over the buttock to the proper angle and secured with adhesive tape. In the case of an annular growth, the tubes must be carried into the lumen of the growth. In using tubes in the treatment of growths occupying only a portion of the lumen of the bowel, a lead plate several millimeters thick may be used over the tubes on the side opposite the growth in order to protect relatively the normal mucosa. In other cases, the normal rectal wall may be packed off by means of a rubber finger cot, to which a catheter is attached. The cot is distended with air after its insertion. In some cases, the application of the radium is made best by the aid of the proctoscope. The quantity of radium employed varies with different operators. Hayward Pinch has used 50 mc. screened with 2 mm. of lead and 2 mm. of rubber. An exposure of thirty hours in periods of six hours each has been given. The course of treatment was repeated in six weeks if thought necessary. With the above dosage, proctitis will be slight or

absent. I favor, ordinarily, the use of a much larger quantity of radium. Many cases may be treated with 200 mc. screened with 2 mm. of brass and 2 mm. of rubber for eight hours. The method of using even a larger quantity of radium for a relatively shorter time is preferable in many cases. If bare emanation ampoules are buried in the growth, the dose of 0.5 to 1 or more mc. of emanation per cubic centimeter of tumor tissue is advisable. When radium treatment for carcinoma of the rectum is contemplated, a preliminary inguinal colostomy is advisable in many cases, although it is not always absolutely essential.

(12) Carcinoma of the Penis, Vulva and Urethra

Carcinoma of the glans penis sometimes responds favorably to radium. Certain cases may be very refractory. We have treated 3 cases in which clinical recovery has occurred. In these cases, amputation of the penis had been previously refused.

Technic of Treatment of Carcinoma of Penis, Vulva and Urethra.—I have used in these cases either surface applications of radium or the insertion of bare emanation ampoules. Two hundred mc. screened with 2 mm. of brass may be applied at a distance of 1 cm. The concentration may be in the ratio of 10 mc. per sq. cm. An exposure of four or five hours may be given. Great care should be taken not to produce severe reactions which may be extremely painful in this situation. If radium emanation in glass ampoules is inserted, the technic previously described may be employed.

Cancer of the vulva may be treated by burying bare emanation ampoules or by surface applications. These two methods may also be combined. Unfortunately metastasis to the inguinal glands is usually an early complication of epithelioma of the vulva. The ultimate outcome is usually unfavorable although the local growth may be healed.

Cancer of the female urethra may be treated by the application of radium tubes to different parts of the growth or by burying bare emanation tubes in its substance. The tumor may be attacked from within the urethra or from the external aspect. The growth may also be reached by radiations from tubes placed along the anterior vaginal wall. Care must be taken not to overexpose the urethral mucous membrane. As it is impossible as a rule to introduce into the urethra a tube covered with sufficient rubber tubing to give an adequate distance of the radium from the growth, a burn of the urethral mucous membrane may be easily caused without producing marked retrogression of the growth. One hundred mc. contained in two tubes arranged end to end, screened with 0.5 mm. of platinum and 2 mm. of rubber may be introduced into the urethra for five hours in several periods of one or two hours each. The external aspect of the growth may be treated in a manner similar to that suggested for epithelioma of the skin. The labia should be widely

separated with gauze during the treatments in order to avoid a burn of these structures. Through the anterior vaginal wall, the growth may be radiated with 200 mc. The concentration of the emanation may be 10 mc. per square centimeter and the screening 2 mm. of brass. The distance should be not less than 1 cm. An exposure of fifteen hours may be given divided into several periods. The radium may be held in the vagina by means of a long silver wire which may be bent to the required angle and fastened with adhesive tape to the anterior abdominal wall. In some cases bare radium emanation tubes may be buried in the growth. The dose of 0.5 to 1 mc. per cubic centimeter of tumor tissue may be used. The different methods of treatment just described may often be advantageously combined.

(13) Carcinoma of the Prostate Gland

Benefit is frequently to be noted from radium treatment of this condition.

Fig. 74.—Adenocpithelioma of the prostate.

The Technic of Treatment of Carcinoma of the Prostate.—Formerly the radium contained in a hollow sound having a wall thickness of 1.5 mm. was introduced into the urethra and allowed to remain in contact with the

growth. At the same time, another tube was introduced into the rectum in order to "cross fire" the carcinoma. While encouraging results have been obtained with this method, no plan seems to be so uniformly successful as that suggested by Barringer. The essence of this method consists in strong central radiation of the prostatic mass.

This author uses 50 mc. of radium emanation, contained in the distal 1½ inches of the lumen of a special gold or steel needle, four to six inches long. Sufficient screening is obtained by the thin wall of the needle. Under local anesthesia, the needle is introduced through the perineum and allowed to remain six hours in each prostatic lobe. If necessary, the

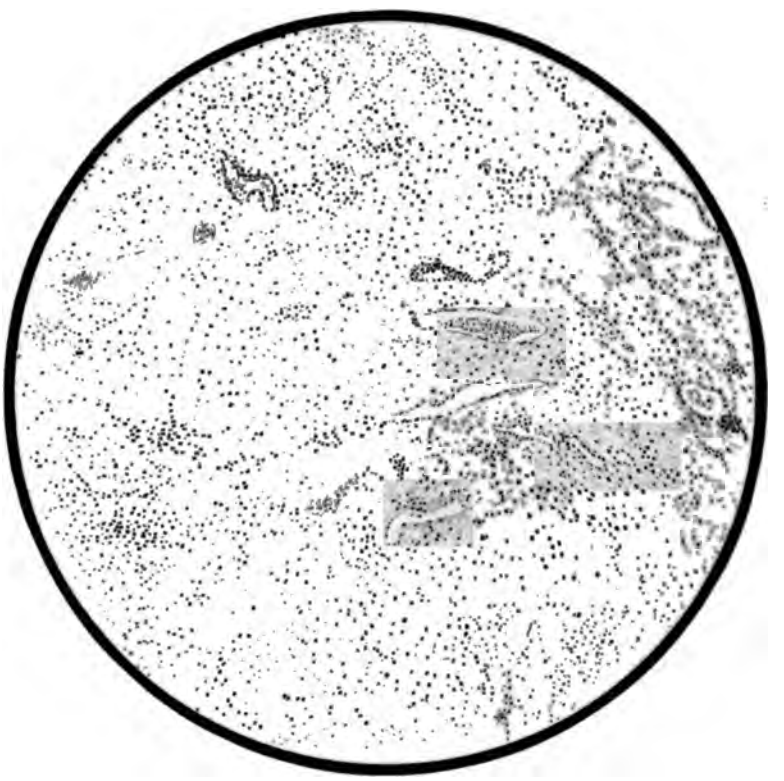

Fig. 75.—Same lesion as in Fig. 74 after radium treatment. Young connective tissue, with newly formed vessels.

needle, guided by a finger in the rectum, can be pushed into the seminal vesicles. In thirty cases treated by Barringer, marked retrogression of the growth followed in every case.

Good results have been obtained by a similar method that I have outlined. This consists in the use of eight or more steel needles each containing about twelve milligrams of radium element or millicuries of radium emanation. These are introduced into the prostate either through a perineal or suprapubic incision in such a manner as to radiate homogene-

ously the entire prostate. One of the writer's cases in which great improvement followed has been reported by R. H. Herbst. The needle introducer illustrated in this report was devised by Dr. O. T. Freer. In carcinoma of the prostate, the general method of needling is the one that promises to be of most value. The method of attack should be adapted to the situation of the growth. Hence, either the suprapubic or the perineal route or both routes may be chosen. The insertion of bare emanation ampoules gives promise of good results.

(14) Carcinoma of the Bladder

Operable Cases.—In dealing with operable cases of carcinoma of the bladder, postoperative radiation is advisable.

Inoperable Cases.—Inoperable carcinoma of the bladder may sometimes be treated successfully with radium. Prior to the use of radium, fulguration is sometimes advisable in order to check the bleeding. The permanent cessation of hemorrhage and the disappearance of cystitis and all subjective symptoms may sometimes be observed as a result of radium treatment. Growths of considerable size may retrogress and ulcerated areas may become covered with healthy epithelium as shown by cystoscopy.

Technic of Treatment of Carcinoma of the Bladder.—Radium may be applied to bladder growths either by way of the urethra or through a suprapubic cystotomy wound. Accurate application to the growth is absolutely essential for success. It is worse than useless to apply radium blindly by means of an ordinary rubber catheter to the interior of the bladder. Special instruments have been devised by Barringer, Corbus, Kanavel, Young, and others for applying the radium through the urethra. Barringer has devised long applicators which may be used in the sheath of a Brown-Buerger operative cystoscope. Young has also devised special instruments for applying radium through the urethra. By means of these applicators, the radium may be held against the growth. Dr. A. B. Kanavel has devised a radium-containing capsule which is provided with a spring clip at one end. One or more capsules may be introduced through an operating cystoscope and attached, in suitable cases, by means of the clip to the surface of the bladder growth. With this device, treatments lasting for any number of hours may be given. The capsule may be removed by means of a silk thread which has been previously attached. The dosage in inoperable carcinoma of the bladder varies with the character of the case and the technic that is employed.

Application through the Urethra.—If the radium is applied via the urethra to the surface of the growth, 100 millicuries, screened with 1 millimeter of silver may be used in periods of one hour each, several times a week, until an exposure of ten hours has been given. A better method consists in the use of two hundred millicuries for five hours. Barringer

has applied in some cases unscreened emanation to the surface of bladder growths via the urethra. The largest dose used by this author was 500 to 1000 millicuries for 650 millicurie hours. In some cases, 50 millicuries contained in a steel needle was inserted into the growth for 100 millicurie hours. In other cases, bare emanation ampoules were buried in the growth.

Application through a Suprapubic Cystotomy Wound.—When accurate application through the urethra, for any reason, is impossible, suprapubic cystotomy may be performed in order to render the growth accessible. Radium tubes may then be introduced through the cystotomy wound and held in position by sutures or by a long pliable silver wire which may be bent to the proper angle and fastened to the abdomen by adhesive strips. Using this technic from 100 to 200 millicuries screened with 2 millimeters of brass and 10 millimeters of rubber may be applied to the growth for from ten to twenty hours in periods of five to ten hours each. In some cases, radium emanation may be inserted into the growth. Five to eight steel needles having a wall thickness of 0.4 mm. and containing 60 to 90 millicuries may be inserted for twelve or eight hours. In other cases bare emanation ampoules may be buried in the growth. In addition to the intravesical treatment, heavily screened radium may be applied to the perineum or inserted into the vagina or rectum in order to cross fire the growth. Care must be taken not to overexpose either of these cavities. In the treatment of carcinoma of the bladder it should be remembered that growths that are superficial may sometimes be successfully treated via the urethral canal. For larger and deeply infiltrating growths, however, the use of large quantities of heavily screened radium at a certain distance from the tumor is imperative. Such cases usually demand that the bladder be opened suprapubically in order to render the tumor accessible. In still other cases, in which the age of the patient or other factors render it inadvisable to open the bladder, palliative treatment may be carried out from the skin surfaces by using large quantities of radium (500 to 1000 or more mc.) heavily screened at a distance of 10 centimeters from the skin.

One of our cases of inoperable carcinoma of the bladder, treated intravesically, which was referred by Dr. M. L. Harris, has been well for more than five years.

(15) Carcinoma of the Breast

Operable Cases.—The policy of declining to treat operable cases of this disease solely with radium should be followed. Preoperative radiation of the breast and its lymphatics followed by operation seems the most logical procedure. Postoperative radiation of the operative field and the areas most likely to harbor metastatic deposits should be carried out. When at least 500 milligrams of radium are available, the thorough saturation of the whole chest wall and its draining lymphatics with deep penetrating rays is advisable. There are certain operable cases in which

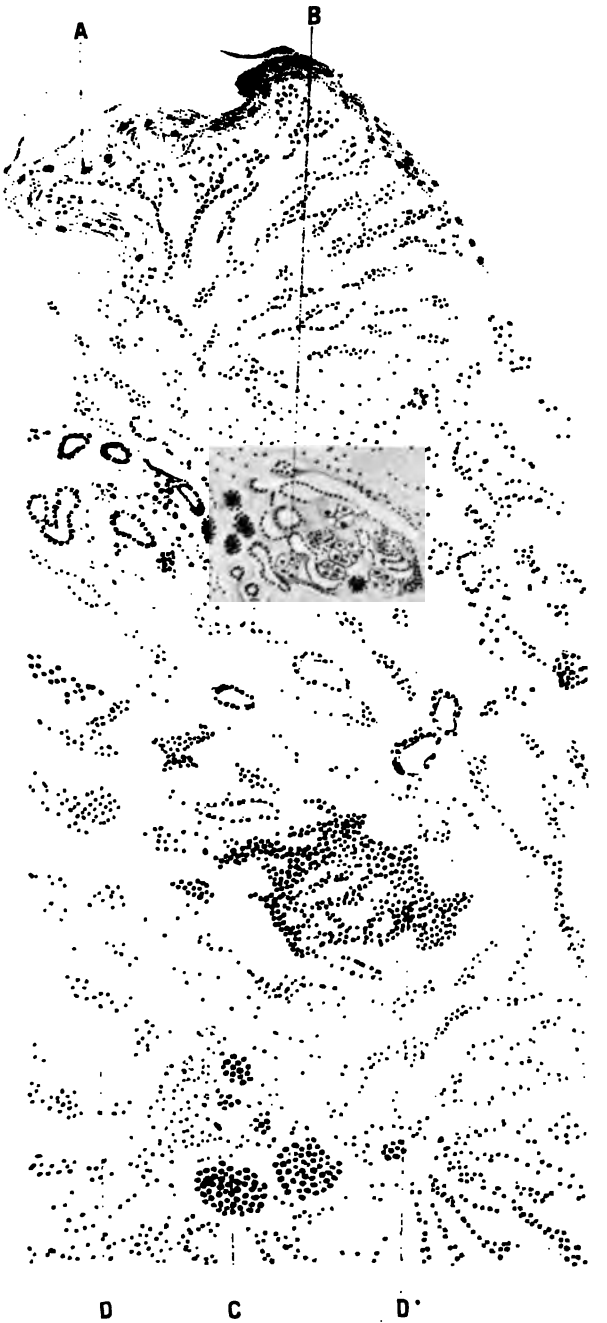

Fig. 76.—Carcinoma of the breast after powerful radiation. The entire section is shown. Slightly enlarged (97 diameters). In this figure are seen, at *B*, glandular elements and the excretory ducts, and, at *C*, the islets of neoplastic origin in the process of destruction. The cancerous islets are situated at a greater distance from the source of the rays than the normal glands, and yet the former exhibit greater effects from the radiation.

The normal glandular elements remain unchanged, while the neoplasm is reduced to a state of degeneration. This illustrates the difference in resistance of healthy and neoplastic tissue.

A, Epidermis reduced to several hypertrophied cells. *B*, Normal glandular elements. *C*, Cancerous islets in the process of degeneration. *D*, Connective tissue stroma of neoplasm. *D'*, Metaplastic connective tissue, uniting and taking the place of destroyed parenchyma.

the patient absolutely refuses to undergo operation. Some of these cases may be successfully treated with radium when the local conditions are favorable. When the breast is not too large and the adipose tissue is not excessive and the tumor itself is small and well localized, success is possible insofar as the local growth is concerned. Unfortunately, metastasis to the regional lymphatics or to distant organs precludes recovery in most cases.

Fig. 77.—Portion of Fig. 76 at *B*. Enlarged 800 diameters.
A, Normal glandular cell. *B*, Supporting tissue. *C*, Lumen of excretory duct. *D*, Epithelial cell bordering upon an excretory duct.

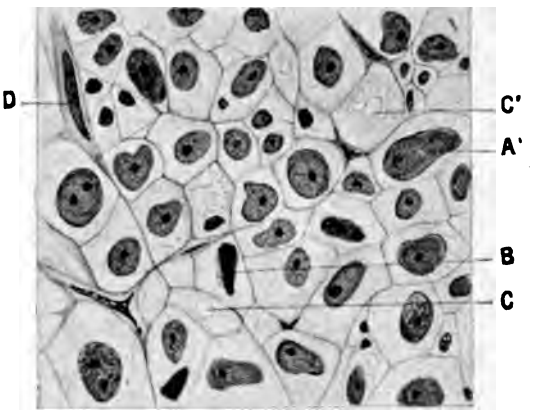

Fig. 78.—Portion of Fig. 76 at *C*, showing carcinomatous cells. Enlarged 800 diameters. The greater part of these cells are in process of degeneration although they have received less radiation than the cells in Fig. 41.
A, Hypertrophied nucleus. *B*, Cell with pycnotic nucleus. *CC'*, Atrophied cell with nucleus absent (Karyolysis). *D*, Young fibroblast penetrating into a degenerated neoplastic islet.

Inoperable Cases.—In cases inoperable on account of the extent of the disease, only palliative treatment as a rule should be undertaken. In cases of the atrophic type, the progress of the disease may be retarded if the more accessible lymphatic glands alone have been invaded. In an inoperable case of this type recently under the writer's care, in which not

only the whole breast but the axillary and supraclavicular glands were involved, complete disappearance of all palpable masses was brought about by radium, but metastasis to the spine occurred. In the more rap-

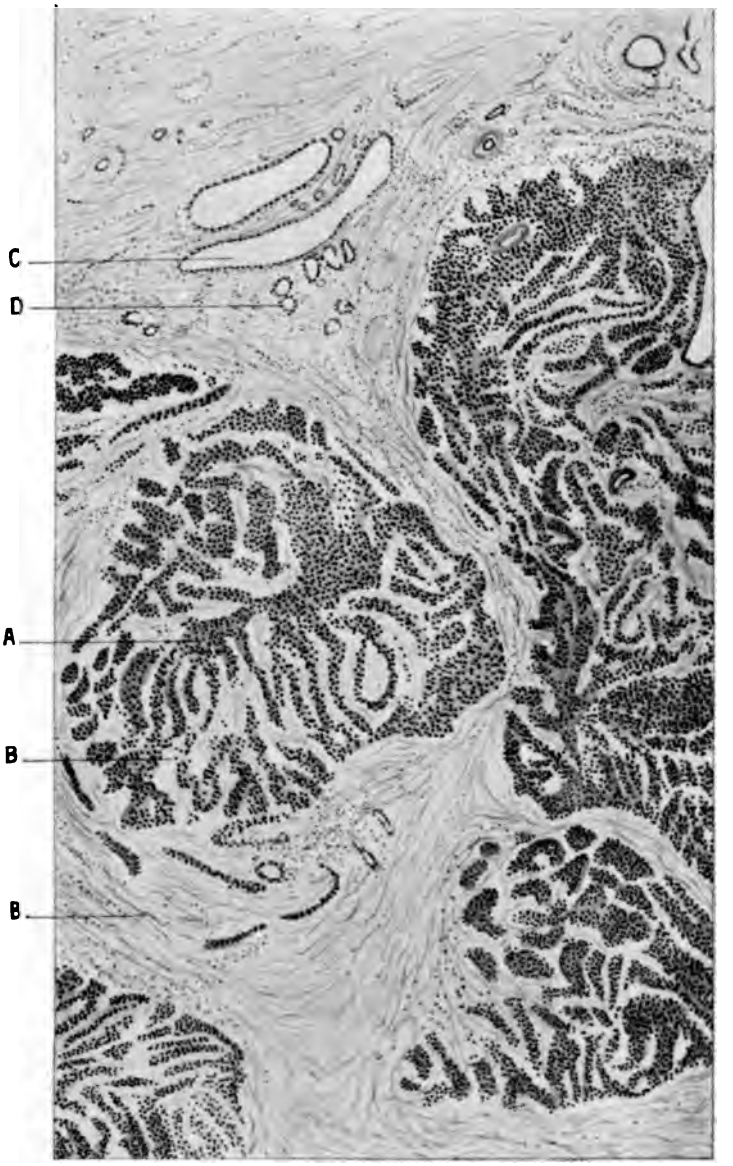

Fig. 79.—Atypic cubical epithelioma of the breast, before radiation. Slightly enlarged (97 diameters).

A, Center of an epitheliomatous lobule. *BB*, Dense connective tissue forming the stroma. *C*, Excretory duct of the mammary gland. *D*, Group of glandular elements.

idly growing type of carcinoma, response to radium treatment is likely to be poor, although pain may be relieved.

Technic of Treatment of Carcinoma of the Breast.—Small cutaneous nodules or superficial ulcerations occurring on the chest wall may frequently be healed by surface radiation. The technic is the same as that for primary epithelioma of grave type involving the skin. Deeper nodules attached to the bone or cartilage of the chest wall may be treated effectively by surface applications or by the insertion into the nodule of a platinum emanation needle containing twenty-five millicuries for eighteen hours. (Hayward Pinch.) In other cases, bare emanation ampoules may be inserted.

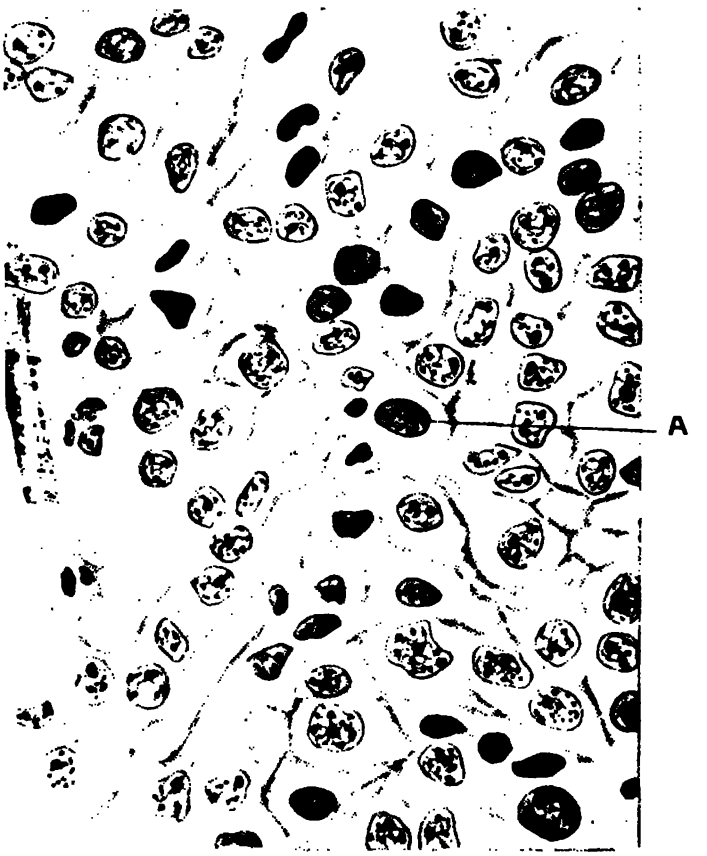

Fig. 80. A part of Fig. 79. Highly magnified (800 diameters). A. Cubic epithelioma tous cell of moderate size, with a single round nucleus and homogeneous protoplasm. Note the absence of connective tissue and the intracellular pseudoparasitic elements in the whole of this preparation which is taken from the center of a lobule. All these cells resemble one another.

When large and deep tumor masses are present, radiations should be of a penetrating character. In some cases, 400 millicuries, screened with 2 millimeters of brass and evenly disposed on a pad 9×12 cm., may be placed at a distance of 6 centimeters. A total exposure of thirty hours in periods of ten or more hours each may be given.

In other cases demanding deep effects, 600 millicuries, screened with 2 millimeters of brass may be placed at a distance of 10 centimeters and

an exposure of thirty hours in periods of ten or more hours each may be given. Sometimes when pleural or peritoneal effusion has supervened in consequence of the involvement of the pleura or peritoneum by the growth, the fluid may be withdrawn and deep radiation immediately given. In some cases, the effusion has not reappeared.

Douglas Quick has recently reported upon the method of burying bare emanation ampoules in the tumor in cases of inoperable breast carci-

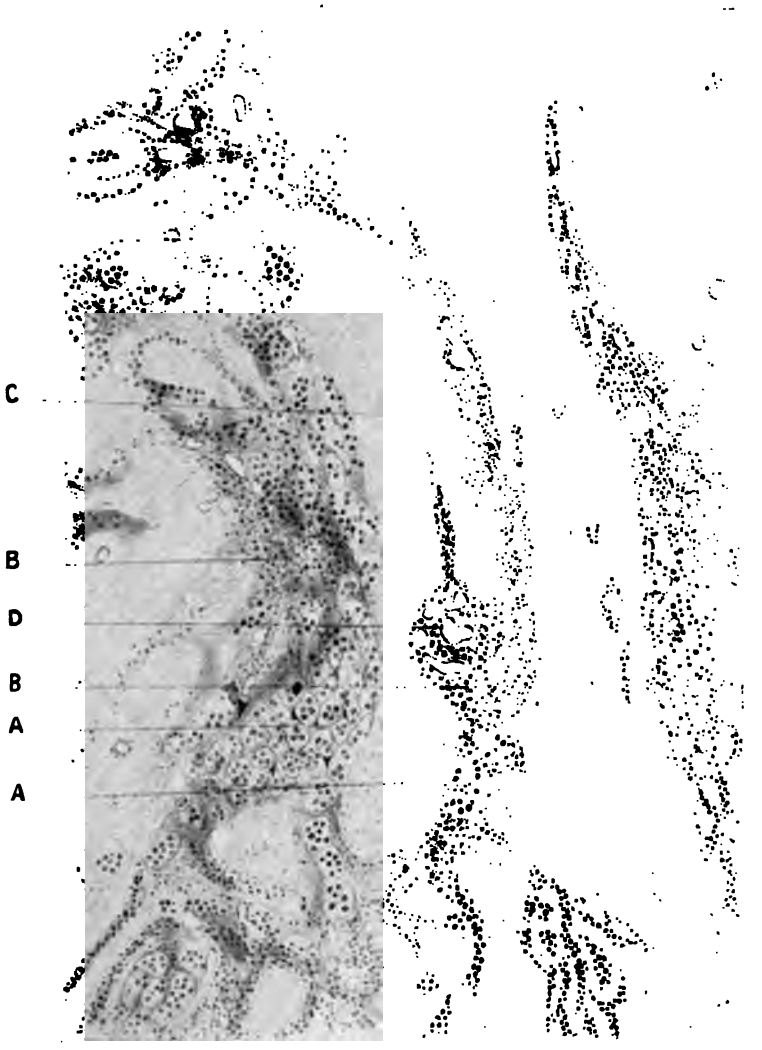

Fig. 81.—Same epithelioma as in Fig. 79, after radiation. Slightly enlarged (97 diameters). Section removed from tissue situated at depth of 2 cm. 10 days after radiation. The elements of the parenchyma are no longer grouped, as in Fig. 79, in lobular masses. These have become invaded and dislocated by young, connective tissue stroma. The epitheliomatous cells are degenerated and swollen—zones of cytolysis. The connective tissue stroma is renewed and is very rich in embryonic elements.

AA, Epitheliomatous cells hypertrophied and degenerated. *BB*, Young connective tissue rich in new cells replacing the tumor elements, which have disappeared. *C*, Dense connective tissue, undisturbed, forming the bed of the primary neoplasm. *D*, Clear zone of cytolysis.

noma coincidently with surface applications of x-rays. Of seventy-eight cases treated in this manner by Quick, seven showed complete regressions for periods of three months to more than two years. Twenty-one cases showed partial regressions. Twenty-four cases received temporary benefit only. Ten cases showed no improvement and nine cases could not be traced. Seven cases were treated during the four months just prior to the report and were not included in the statistics, although the initial response to the treatment was favorable. Russell Boggs has also reported favorable results from the insertion of steel needles containing

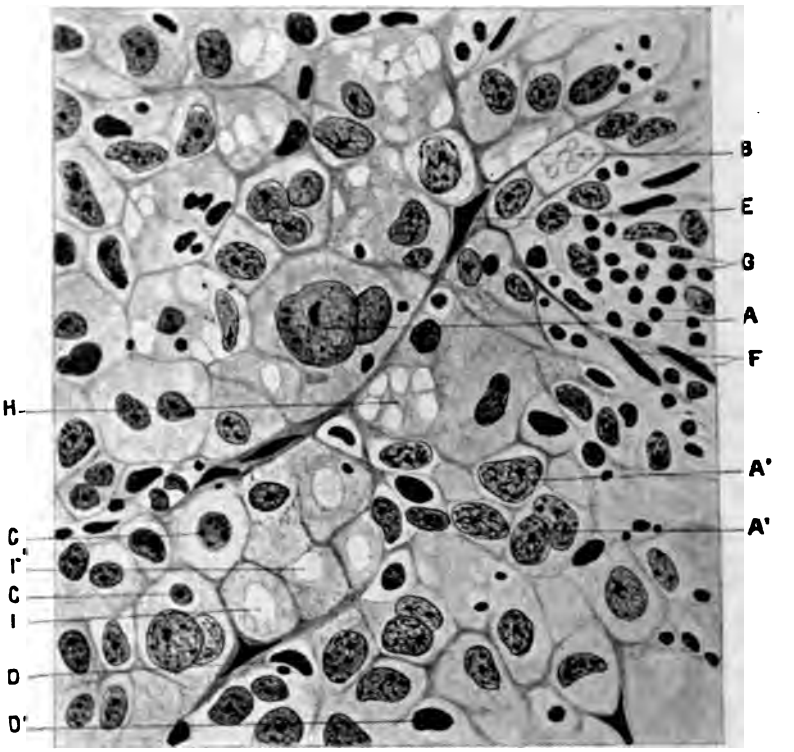

Fig. 82—A part of Fig. 81. Highly magnified (800 diameters). Note here the polymorphism of the tumor elements, their hypertrophic and malformed nuclear structures. The epitheliomatous nodules are infiltrated with a vascular connective tissue development in a state of paraembryonic metaplasia. Notice the presence, interspersed amongst the epitheliomatous cells, of large, star-shaped anastomosing connective tissue cells.

A, Hypertrophied epitheliomatous cell with a giant nucleus. *A'A'*, Cells with multiple nuclei. *B*, Capillaries, newly formed at the edge of the infiltration. *CC*, Pseudoparasitic bodies. *DD'*, Pycnotic nuclei. *E*, Star-shaped connective tissue cell joined to its neighbors by protoplasmic elongations. *F*, Young fibroblasts from the infiltration tissue. *G*, Mononuclear leucocytes interspersed in the infiltration tissue. *H*, Cell with vacuoles without nucleus in state of cytolysis. *H'*, Cell deprived of its nucleus (karyolysis).

radium salts into breast carcinomata combined with the use of surface radiations with x-rays.

In the report of the London Radium Institute for 1919, ninety-five cases of cancer of the breast were mentioned that had applied for treatment during the year. Seven cases were examined but not treated; no recent

report had been received from 12 cases; 5 cases received prophylactic treatment; 50 cases were improved; 13 were not improved; 2 abandoned treatment; 4 died and 2 were apparently cured.

Between January, 1914, and January, 1921, the writer treated 90 cases

Fig. 83.—Carcinoma of left breast. This tumor measured 16x12 cm., and was elevated about 5 cm. above the level of the skin. Photograph taken October, 1919. Patient referred by Dr. A. J. Auner.

of breast carcinoma of different types. Eighty-five of these cases were primarily inoperable or inoperable recurrences. Five cases were treated that were operable so far as the disease was concerned, but inoperable

on account of other conditions. In 30 of the 85 inoperable cases just referred to, palliation only was attempted, the process being too far advanced to permit of expectation of regression. Of the remaining 55 cases of this group, 6 showed complete clinical regression, 29 were definitely improved, 10 were not improved to a marked extent and 10 abandoned treatment. One of the earliest cases of clinical regression

Fig. 84.—Patient in Fig. 83, showing improvement under radium treatment. Photograph taken May, 1920. At this time, the patient was free from macroscopic carcinoma. The open area at the site of the former growth was the size of a 25 cent piece but was not carcinomatous. The small swelling at the junction of the arm and chest is merely a fold of skin. Complete healing occurred later. Patient was living and in good health one and one-half years after photograph was taken. Recently we have learned patient's health is failing.

that we obtained was mentioned by the writer in a previous article (Illinois Medical Journal, August, 1916). The patient referred to in the above report died later, probably from spinal metastasis, but her condition was rendered comfortable and her life was apparently prolonged for about four years.

Of the 5 operable cases that I have treated, 3 made a complete clinical regression that has been maintained for periods of from six months to two years. One case was refractory and one case abandoned treatment, after an initial marked improvement was noted in both instances.

Improvement in the technic, such as the use of more massive doses of radium at a considerable distance from the skin combined with the implantation of bare emanation ampoules has led to better success in the last few years than was formerly thought possible.

(16) Carcinoma of the Cervix Uteri

Operable Cases.—In the treatment of operable cases of cancer of the cervix, it was the general opinion until recently that hysterectomy with preoperative and postoperative radiations was the method of choice. Janeway and others have lately expressed the opinion that radium treatment alone, in certain cases of operable cancer of the cervix, is now justified. Some authors even state that operation in cancer of the cervix should be replaced by radium. We have already referred to the fact that Bumm, Doederlein and Kroenig have taken this position and have abandoned operation in favor of radium treatment in all cases of cervical cancer. Schaefer, a coworker of Bumm, has reported the following results: Of 155 cases of cancer of the uterus treated with radium which were either operable or on the borderline of operability, recovery occurred in 83 (53.54 per cent). Seventy-four of these cases were operable. Of these, 48 (66.21 per cent) were well after periods of one to three years. The foregoing results may be compared with the results of operation in 203 cases reported by the same author. In this series 98 (48.27 per cent) were well after periods of one to three years. Radiation seemed therefore to give results better than those obtained by operation. On the basis of these results, Schaefer has also abandoned operation for radiation in cervical cancer.

Borderline Cases.—In cases in which the surgeon is in doubt as to the advisability of operation, radium treatment is undoubtedly the preferable procedure. In these cases, long experience has shown that operative interference is not followed by good results. In some cases in this category and even in some cases that are strictly inoperable, radium treatment may render the case operable. It is probably best, however, not to attempt to remove the uterus when a clinical recovery has occurred under radium.

Fig. 85.—Metatypic pavement cell epithelioma of the neck of the uterus. Before treatment. (Enlarged 180 diameters.)

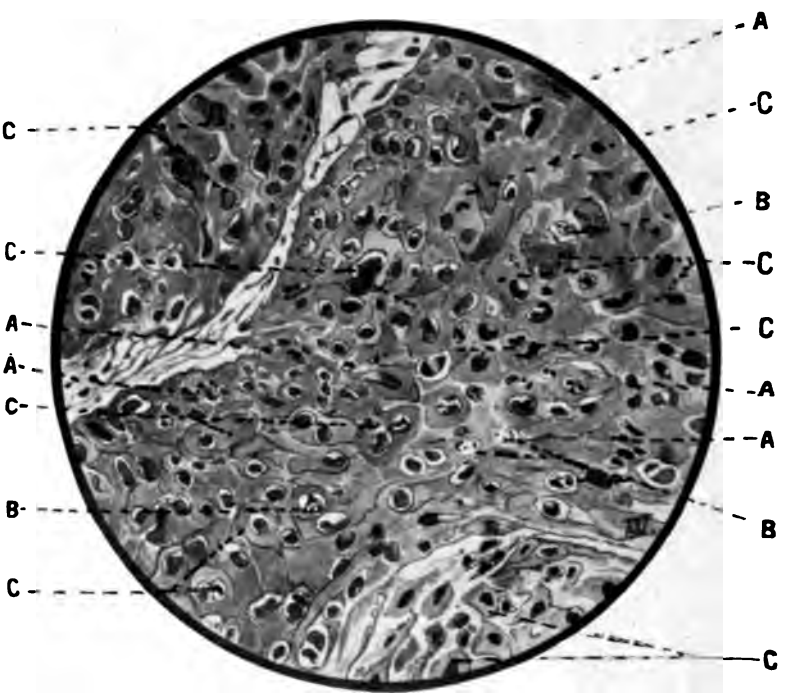

Fig. 86.—Same epithelioma as in Fig. 85. Fragment removed 10 days after the first application of radium. (Enlarged 180 diameters.)

A, Cells that have not as yet undergone any changes. *B*, Cells influenced by the radiation and already showing signs of necrosis; (nucleus retracted in pycnosis—the chromatic substance scattered in the cytoplasm). *C*, Cells hypertrophied in varying degrees with irregular, often monstrously budded, nuclei.

Inoperable Cases.—"Uterine cancer continues to yield most gratifying results and the effect of radium treatment in inoperable cases is far in advance of those obtained by any other known medical or surgical methods." (Report of the London Radium Institute.) Certain authors are of the opinion that 25 per cent of inoperable uterine and vaginal cancer can be cured by radium.

The clinical improvement of the majority of cases of carcinoma of the cervix under radium is striking. Cessation of the hemorrhage and foul discharge and relief from pain are very frequently obtained. Disappearance of fungating masses and healing of ulceration are often noted. In

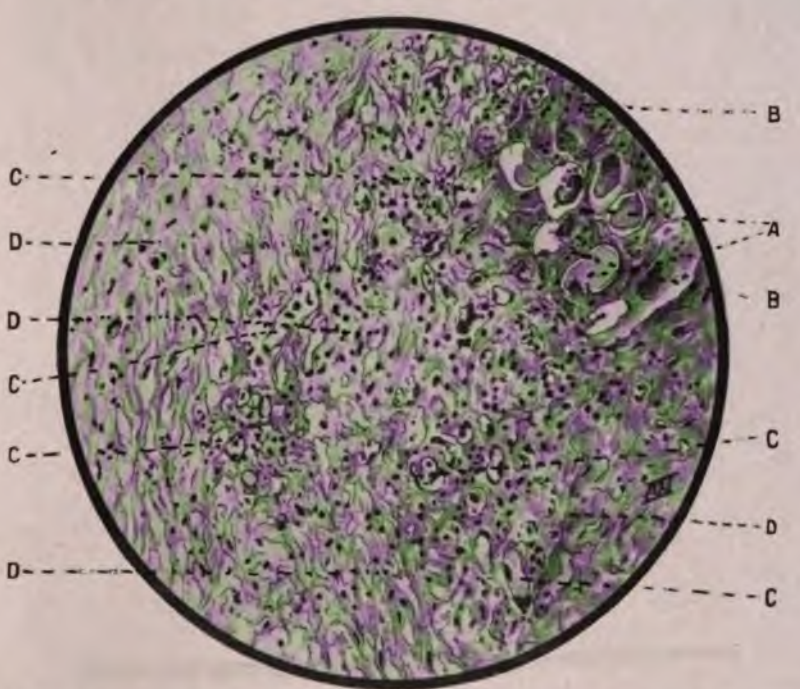

Fig. 87.—Same epithelioma as in Fig. 85. Section removed on the 29th day after the first radiation. (Enlarged 180 diameters.)

A, Group of hypertrophied epitheliomatous cells, degenerated, in process of disappearance (karyolysis, plasmolysis, cytolysis), imbedded in and infiltrated with: *B*, Embryonic and polynuclear cells. *C*, Remains of necrotic cells intermingled with polynuclear cells which disorganize and absorb them. *D*, Young connective tissue rich in embryonic cells, fibroblasts, plasma cells; the beginning of a cicatrization occupies the larger portion of the preparation.

some cases, palliation only is to be expected. In a few cases, no improvement is obtained.

The Technic of Treatment of Carcinoma of the Cervix.—The technic of treatment naturally varies with different cases, and indeed almost every experienced worker with radium has, to some extent, an individual method. The difference in technic is quite remarkable and illustrates the toleration of the cervix uteri and adjacent tissues to radium treatment. It is noteworthy, however, that the enormous doses formerly rec-

ommended by some writers have been attended not infrequently by untoward sequelae and particularly by rectovaginal and vesicovaginal fistulae. The present tendency is toward moderate dosage in or against the cervix.

A review of the different methods as practiced by Bumm, Cheron-Duval, Clark, Degrais, Janeway, Kelly and Burnam, Hayward Pinch, Schmitz, Wickham and many others, seems to demonstrate clearly that moderate dosage brings about the local disappearance of the cancer quite as well as enormous doses and without the untoward effects that may attend the use of very large quantities of radium. We believe also that several

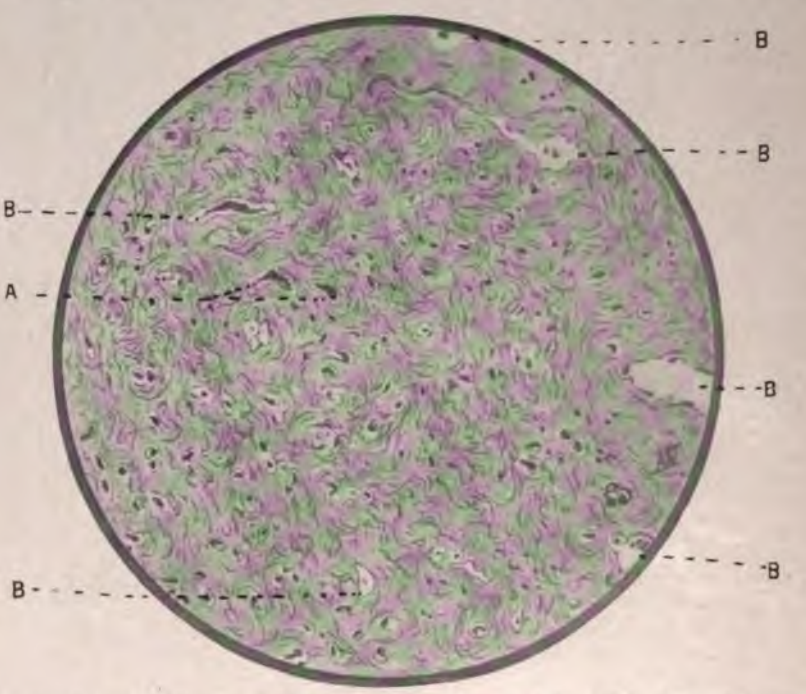

Fig. 88.—Same epithelioma as in Fig. 85. Fragment removed from the surface of the cicatrix of the neck of the uterus three months after first radiation. Dense connective tissue, rich in cellular elements.

A, Well developed, star-shaped connective tissue cells. *B*, Newly formed capillaries.

treatments are often preferable to a single treatment, although the effect may not seem quite so brilliant. Whether a certain amount of curetting should precede radium treatment in order to remove fungating masses is debatable. We believe it is not advisable. We are opposed to preliminary cauterization undertaken for the same purpose. In the technic of treatment much depends upon the distribution of the radium with reference to the growth. When the radium is not too concentrated per unit area, larger doses are naturally tolerated.

We shall mention at this time the technic of only a few therapeutists.

Burrows (Manchester and District Radium Institute) gives an exposure

of 3000 millicurie hours. He buries in the growth 5 to 7 platinum tubes (wall thickness 3/10 mm.) containing 120 millicuries and allows them to remain twenty-four hours.

Hayward Pinch (London Radium Institute) gives a total exposure of about 1600 millicurie hours. One tube of not less than 53.6 mc. is introduced, if possible, into the cervical canal, and if this is impossible, into the posterior vaginal fornix. The screening is 2 mm. of lead plus 2 mm. of rubber. Several treatments are given—the duration of the entire treatment being twenty-four to thirty hours.

Janeway advises in average cases an exposure of 6000 millicurie hours. He used 300 millicuries in 3 tubes inside the uterus and 3 tubes containing 200 millicuries over the cervix. The screening is the equivalent of 3 millimeters of lead plus rubber. One treatment of twelve hours is given. More recently he has inserted, in addition, bare emanation tubes into the cervix.

Schmitz gives a total exposure of 2000 to 2400 milligram hours in the cervix and later the same dose against the cervix. He uses fifty milligrams screened with 1.2 mm. of brass.

My technic in average cases has consisted in giving an exposure of about 3000 millicurie hours. In suitable cases, 200 millicuries screened with 2 mm. of silver are introduced into the cervix for seven and one-half hours. Two subsequent exposures of fifteen hours each with 50 millicuries screened with 2 mm. of silver plus 2 or more mm. of rubber against the cervix are then given at intervals of three or four days. It must be emphasized that there is no one technic adapted to all cases and that equally good results may doubtless be obtained in the same class of cases by different methods. In addition to the intrauterine and intravaginal exposures, it is imperative to use powerful deep radiations over the abdomen and sacrosciatic notches. Three portals of entry may be mapped out on the abdomen. Five hundred to 1000 millicuries screened with 2 mm. of brass may be applied over each portal at a distance of 6 or 10 centimeters for twenty-five or eighteen hours in periods of ten or more hours each. The emanation may be arranged on a pad having a superficial area of 100 square centimeters. The splenic area should be carefully protected during the abdominal radiations.

In carrying out intravaginal treatment, it is important to pack off well the posterior vaginal wall, as the rectum is especially sensitive to radium rays. Treatment may otherwise be followed by proctitis.

When treatment is undertaken for recurrences after extensive pelvic operations, the quantity of radium used in the vagina should be reduced by one-half and the time of exposure by one-fourth, otherwise the radium may cause at times a destructive and intractable reaction. Following intravaginal radium treatment, douches should be systematically given for at least six or eight weeks to prevent the formation of adhesions. A

second series of treatments six or eight weeks after the first series may be advisable but these should always be of less intensity. Too powerful or too frequently repeated exposures may result in painful and destructive reactions which may appear many months after the treatment is discontinued.

From the standpoint of treatment, Dr. John G. Clark draws a sharp distinction between cancer of the cervix and cancer of the fundus uteri. In the former condition, he advises the use of radium; in the latter, he advocates hysterectomy even though the disease is advanced. Many authors advise the use of radium in all borderline and advanced cases of cancer of the uterus, irrespective of its location.

Results of the Radium Treatment of Uterine Cancer.—The literature of the subject has grown to such great proportions that we shall mention the results of only a few authors. Many additional references will be found in the bibliography.

In the course of five years, H. Cheron and Rubens-Duval treated 158 cases of primary and recurrent inoperable uterine and vaginal cancer. In 155 cases there was improvement that was anatomically verified. In 93 cases, the improvement was marked. The authors state that in 46 cases there was probably a definite cure. In only 2 cases was the treatment without appreciable good effect.

These authors have also reported a case that may be mentioned as showing the possibility of a complete anatomical cure of localized cancer with radium. The patient referred to suffered from inoperable cancer of the uterus and made an apparent recovery under radium. Fifteen months later the patient died of another disease and histological examinations of the various organs of the body showed no trace of cancer.

Kelly and Burnam have reported a series of 213 cases of cancer of the uterus treated with radium in which the results are thus summarized by the authors: "Out of 213 cases treated, 14 were operable and 199 inoperable.

"Operable cases: Of the 14 operable cases, 10 patients were operated on and treated prophylactically with radium. Of these, 2 have been well for more than three years, 1 for more than two years, 4 for more than one year, and 3 for more than six months. The number is too small from which to draw conclusions, and yet is suggestive when we consider that in 75 per cent of all cases with operation there is recurrence and that 60 per cent of these recurrences take place within one year following the operation.

"In four cases of the operable group, on account of some general contraindication to operation, radium alone was used. All of this group are living and well; two for over three years and two for over one year.

"Inoperable cases: The total number of inoperable cases and inoperable recurrent cases is 199, of which 53 patients have been clinically cured, 109 markedly improved and 37 not improved.

"Our series includes 35 of originally inoperable cancer of the cervix uteri or vagina in which the patients are clinically cured, in 2 cases for over four years, in 2 cases for over three years, in 4 cases for over one year, and in 10 cases for over six months. It also includes 18 cases of originally inoperable recurrent cancers in which the patients are now clinically cured; in 1 case for over six years, in 1 case for over four years, in 11 cases for over two years, in 10 cases for over one year and in 5 cases for over six months. Excluding the operable cases, in which we have both operated and used radium, there are 203 cases left; in 57 of these 203 cases the patients are 'clinically cured.' We will reserve the word cured for later reports, to apply to cases beyond the five year limit, which has been conventionally adopted by surgeons as a time limit for estimating the permanency of cures of malignant disease. Of the 57 clinical cures, 1 has lasted for six years, 3 for over four years, 4 for over three years, 5 for over two years, 29 for over one year, and 15 for over six months."

F. J. Taussig has recently collected the available literature dealing with five year radium cures of cervical cancer. Out of 1114 cases, operable and inoperable, reported by twelve authors in different countries. 223 were said to be well after five years (about 20 per cent). Out of 415 operable cases, 131 were well after five years (about 31 per cent).

Between January, 1913, and January, 1921, the writer treated 138 cases of carcinoma of the cervix. These cases may be divided into three groups.

(a) Primary doubtfully operable, i.e., "borderline"—10 cases.

(b) Primary inoperable—88 cases.

(c) Inoperable recurrences after operation—40 cases.

Of the 10 borderline cases forming the first group, we have reports from 6. Three of these are living after more than three years and 3 are dead.

Of the 88 primary inoperable cases forming the second group, reports have been obtained from 45. Twenty-eight of these are living and 17 are dead. Twelve of the living cases are well after more than three years. It may be stated, however, that in this group of inoperable cases there were 12 in whom palliation alone was attempted.

Of the 40 inoperable recurrences forming the third group, we have reports from 20. Of these 8 are living and 12 are dead.

Of a total of 138 doubtfully or wholly inoperable cases, 51 have been lost sight of. Eighty-seven have been traced, of whom 30 are living and 57 are dead. If we assume that none of the untraced cases is living the proportion of clinical recoveries for more than three years is slightly more than 21 per cent.

In the majority of all of our cases, except those in which palliation only was attempted, local healing occurred under radium, and life was prolonged and made bearable.

SARCOMATA

When treated early and before dissemination to various parts of the body has occurred the results of radium treatment in sarcomata are on the whole beneficial. Unfortunately, the occurrence of metastasis may sooner or later render the prognosis unfavorable, but numerous cases have remained well for considerable periods of time.

Different types of sarcomata exhibit marked variations in their radiosensibility. Lymphosarcoma is particularly sensitive to treatment. It is one of the most gratifying of all growths in its response to radium. In this type of disease, large tumors which may affect the neck, mediastinum, retroperitoneal lymph glands, etc., may disappear in the most surprising fashion.

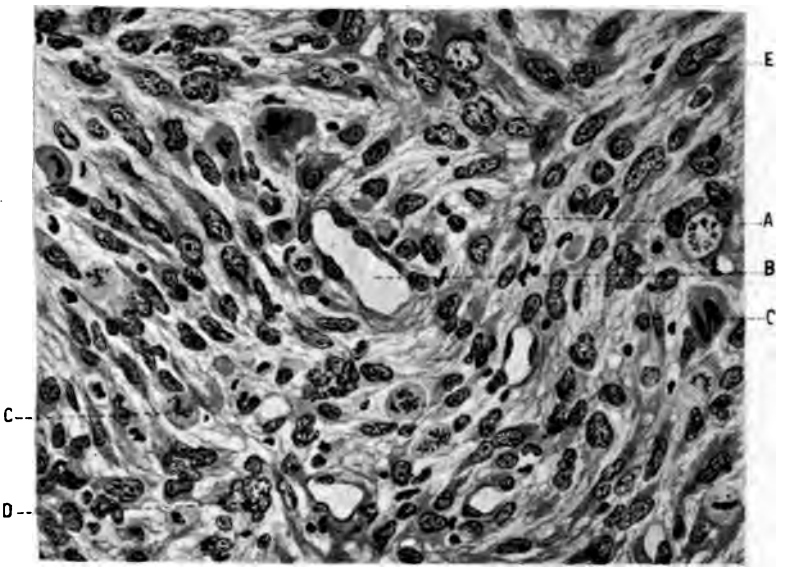

Fig. 89.—Polymorphous sarcoma with predominance of fusiform cells. Before radiation (enlarged 400 diameters). The chromoplasm of the cells is quite abundant, forming a mesh-like network filled with hyaloplasm, with no elaboration of the collagen.

A, Fusiform cell. *B*, Vessel lying in sarcomatous tissue and bordered by tumor elements. *C*, Cells in atypic karyokinesis. *D.E.*, Plasma cells.

In a type of tumor usually referred to as sarcoma but classed by Janeway and Ewing as "teratoid carcinoma of the testis and ovary" a remarkable susceptibility to radium is seen. Janeway has reported a number of cases successfully treated.

In one of the writer's cases, referred by Dr. W. A. Stuhr, which was probably of the type just mentioned, a large mass was present in the right hypochondrium. The tumor extended from the costal arch to the umbilicus and was apparently larger than a child's head. This growth had been preceded a year before by a sarcoma of the right testis which had been surgically removed. Complete disappearance of the abdominal

tumor occurred within a few weeks under radium treatment. The patient is now in excellent health after more than three years.

Melanosarcoma is not, as a rule, favorably affected by radium but in exceptional cases may yield completely.

We may refer briefly to sarcomata occurring in different situations.

(1) Sarcoma of the skin is usually amenable to radium treatment.

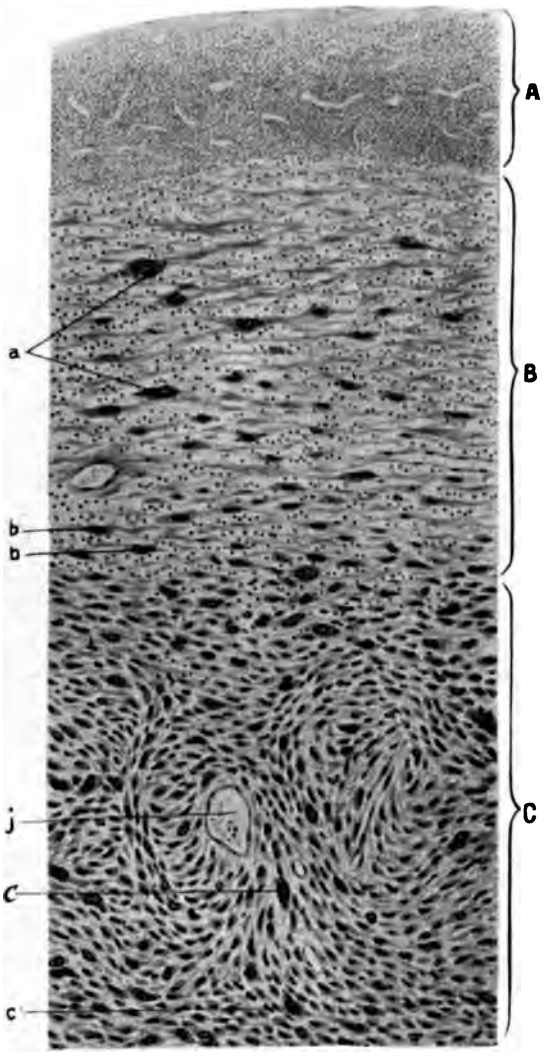

Fig. 90.—Same sarcoma as in Fig. 89. Section of large nodule removed 15 days after powerful irradiations. Slightly enlarged (80 diameters).

Zone A, Superficial part, in contact with the apparatus; zone of massive necrosis.

Zone B, Showing cellular monstrosities and phagocytes. Sarcomatous elements scanty but quite bulky and in state of degeneration. Numerous leucocytes.

Zone C, Showing stratum of least modifications—nevertheless the sarcoma is modified. Hypertrophied forms of cells of monstrous shapes.

a, Monstrous degenerated cells. *bb*, Elongated sarcomatous elements having a resemblance to young fibroblasts. *cc*, Multinucleated plasma cells. *j*, Sarcomatous vessels.

(2) Periosteal sarcoma is frequently benefited by radium.

(3) Sarcomata of the tonsil and postnasal space are frequently amenable to radium and very striking results are sometimes obtained. I have treated in conjunction with Dr. O. T. Freer three cases of sarcoma of the postnasal space in which recovery occurred. Two of these cases have remained well for more than three years. In one case, late glandular involvement proved fatal.

(4) Sarcoma of the larynx may be treated in a similar manner to that suggested for carcinoma.

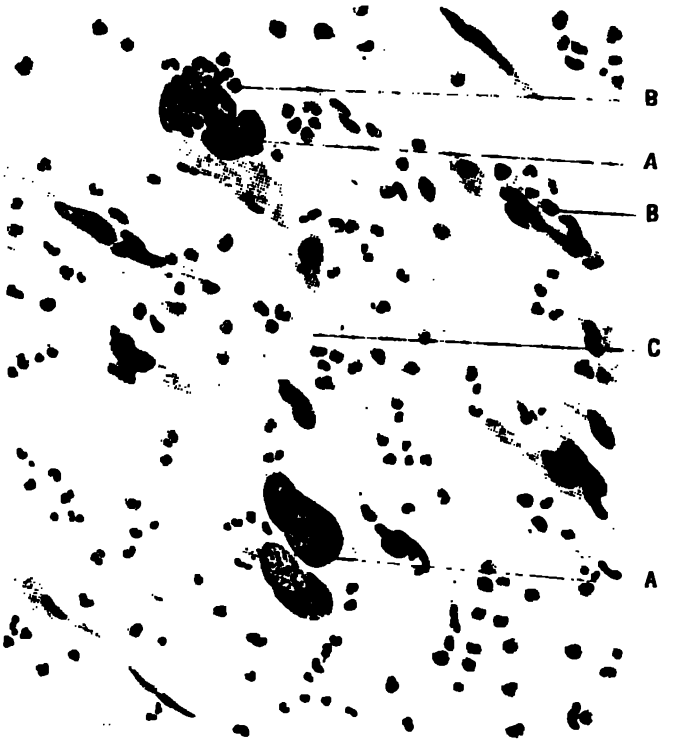

Fig. 91. Same sarcoma as in Fig. 89. After radiation. Highly magnified (490 diameters).

This section shows a portion of zone B in Fig. 90 and illustrates the extraordinary volume, and the strange forms of the sarcoma elements under the influence of the radiation before they disappear by phagocytosis. The relative scarcity of neoplastic cells is plainly discernible.

A. Greatly hypertrophied sarcomatous cells with multiple or polylobular nuclei, with protoplasm acidophilous, invaded by polynuclear leucocytes. *B.* Neutrophile polynuclear leucocytes [illegible] the protoplasm of the degenerated sarcomatous cells. *C.* Fibrillar stroma infiltrated [illegible].

5. Sarcoma of the orbital tissue recurring after operation is often benefited by radium. Unfortunately, metastasis to the neck or distant organs occurs sooner or later in most of the orbital cases.

6. Mediastinal sarcoma. Numerous instances of mediastinal tumor have received great benefit from radium treatment. It is probable that many mediastinal growths are lymphosarcomata and the excellent results sometimes noted after radium treatment may be explained by this fact. Burnam has reported an interesting group of 8 cases of mediastinal

Fig. 92.—Sarcoma of right ear. Recurrence after excision. Photograph taken September, 1915.

Fig. 93.—Patient in Fig. 92 after radium treatment. Photograph taken November, 1915. A recurrence took place in glands of neck in March, 1916, which was found to be inoperable. Recovery occurred under radium treatment. Patient was well 5 years later.

tumor treated with radium, in which the greatest improvement occurred in all but 1 case.

The Technic of the Treatment of Sarcoma.—The method of treatment varies greatly according to the situation and size of the tumor. In postnasal cases, 100 mc, or more, screened with 1 mm. of silver plus 1 mm. of rubber may be used. Contained in two tubes placed end to end, the

Fig. 94. Sarcoma of left cheek in girl aged nineteen. Photograph taken May 17, 1921. Patient referred by Dr. O. T. Roberg.

radium may be applied through the anterior nares for six hours in several periods of two or three hours each. The treatments may be given every day or on alternate days. In tonsillar sarcoma, radium needles may be buried in the growth (60 mg. in 5 needles, $\frac{1}{10}$ mm. screen, 8 hours), or bare emanation tubes may preferably be used. In orbital sarcoma, 100 mc., screened with 2 mm. of brass may be inserted into the orbital cavity for six hours. This treatment should follow evisceration

or exenteration either at the time of the operation or in the event of recurrence. In all types of deep sarcoma or when large masses exist, deep raying with large quantities of radium is the method to be chosen. Five hundred or 1000 mc., to each 100 square centimeters, screened with 2 mm. of brass and placed at a distance of six or ten centimeters may be applied. At a distance of 6 cm., 12,500 mc. hours and at a distance of

Fig. 95.—Patient in Fig. 94 after radium treatment. Photograph taken Oct. 20, 1921. Metastases to the skin of the right breast, abdomen and thighs occurred later. These disappeared under radium. In December, 1921, patient appeared clinically well. In February, 1922, we learned that patient's health was failing.

10 cm., 18,000 mc. hours may be given. In mediastinal tumors, Kelly and Burnam have used more than a gram of radium at a distance of from 1½ to 6 inches, for periods of four or more hours on each area.

Pancoast has reported some encouraging results following the radium treatment of brain tumors (sarcoma, glioma, endothelioma, pituitary tumors).

Fig. 96.—Tumors of eyelids. Microscopic section showed lymphoma (?). Photograph taken July, 1920. Patient referred by Dr. Wm. A. Fisher.

Fig. 97.—Patient in Fig. 96 after radium treatment. Photograph taken September, 1920. Patient was well one and one-half years later.

Fig. 98.—Sarcoma of bone. Recurrence after operation. Patient referred by Dr. A. B. Kanavel.

Fig. 99.—Patient in Fig. 98 after radium treatment. Improvement was only temporary.

Fig. 100.—Lymphosarcoma of neck. Photograph taken July, 1919. Note scar of previous operation.

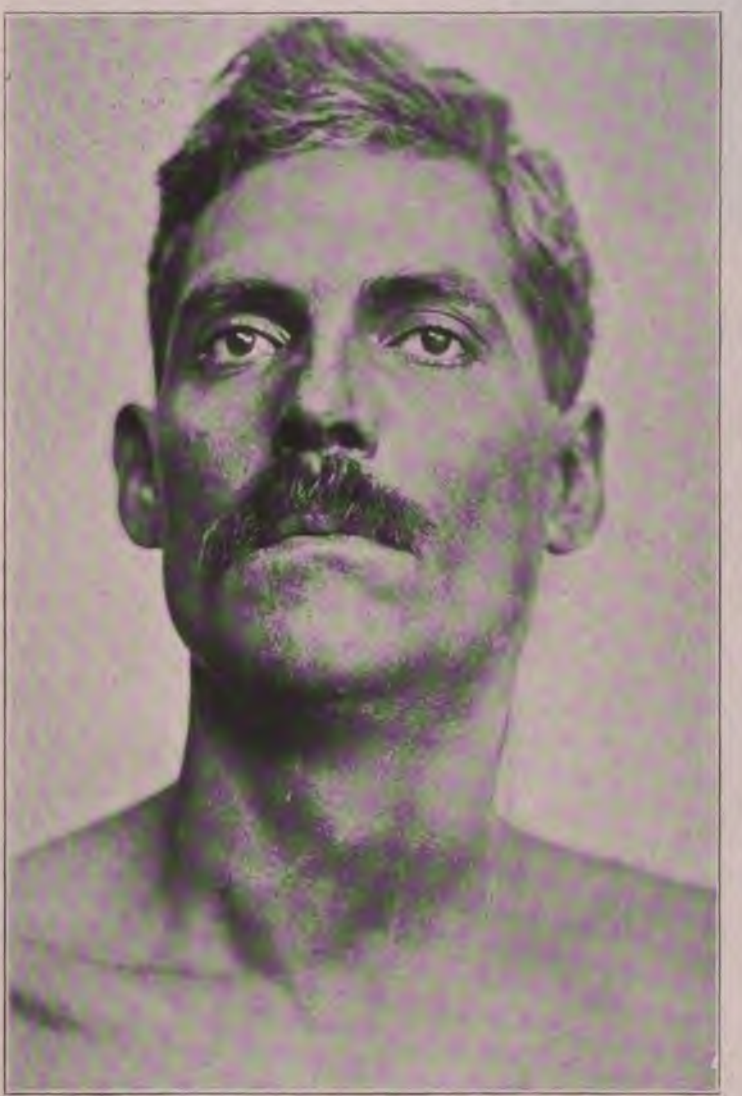

Fig. 101.—Patient in Fig. 100 after radium treatment. Photograph taken in December, 1919. Later recurrences took place in throat, axillae, inguinal regions and abdomen which yielded for a time to further treatment. The patient had about a year of comfort as the result of the treatment.

B. BENIGN TUMORS

The treatment of keloids, nevi, etc., will be considered in the chapter devoted to Radium in Dermatology.

The treatment of fibromyomata of the uterus will be considered in the chapter on Radium in Gynecology.

C. CHRONIC INFECTIONS

Tuberculosis

Tuberculosis of the skin will be considered under Radium in Dermatology.

Tuberculous Adenitis

In the early stages of tuberculosis of the lymphatic glands, radium treatment frequently causes a diminution in size of the glands and sometimes brings about a clinical recovery. Moderately deep radiations should be given. Two hundred millicuries distributed in the ratio of 1½ mc. per square cm. screened with 2 millimeters of brass and placed at a distance of 3 centimeters may be employed for thirty hours in periods of ten or more hours each.

Tuberculous Sinuses

On numerous occasions we have introduced 25 to 50 milligrams contained in two or more tubes screened with one mm. of silver along the course of tuberculous sinuses leading to the bone. A total exposure of four to eight hours has been given. Improvement has sometimes followed. Other authors have reported the healing of such sinuses.

In military surgery, Cameron has seen improvement follow the introduction of a radium tube containing 10 milligrams screened with one millimeter of silver into chronic sinuses for periods of ten to thirty minutes repeated several times at intervals of two to four days.

Actinomycosis

Actinomycosis has been treated with radium by Heyerdahl who has reported six cases. Four of these were clinically cured and two were improved.

CHAPTER XVI

RADIUM IN GYNECOLOGY

A. MALIGNANT TUMORS

The treatment of carcinoma of the uterus, the labia, the urethra, etc., has already been considered in the chapter on Radium in General Surgery.

B. BENIGN TUMORS

Fibromyoma of the Uterus

Dr. Robert Abbe, of New York, was the pioneer in the use of radium in fibromyoma of the uterus. His first case was treated in 1905 by the introduction of radium into the interior of the uterus. In proper cases, radium treatment of uterine fibroids is now a routine procedure with those who have had experience with the method. Abbe, J. G. Clark, Degrais, Hayward Pinch, Kelly, Schmitz, Stacy, Wickham and many others have used radium extensively in this condition. Kelly has reported a series of 210 cases. Clark has observed more than 150 cases. I have treated over 60 cases. While there is general agreement as to the beneficial results of treatment, there are naturally some differences of opinion as to the class of cases in which radium is most suitable. With our present experience, we believe that one is justified in using radium in all cases of fibromyoma that are causing symptoms unless a positive contraindication is present. Clark believes that fibroids in young women should be radiated with great caution on account of the possibility of bringing on an abrupt and serious menopause. He ordinarily limits the use of radium therefore to cases occurring within the menopausal cycle. Kelly apparently does not recognize an age limitation. Sixty-four of his cases were under forty and in twenty-eight of these, the tumor practically disappeared. The presence of acute or quiescent inflammatory conditions in the pelvis is a positive contraindication. Clark believes that when the tumor is larger than a three months' pregnancy, operation is to be preferred. Dr. L. J. Stacy of the Mayo Clinic also believes that very large fibroids should be operated on and draws attention to the possibility of mistaken diagnosis and of unrecognized carcinoma of the fundus. Many authors do not regard the size of the tumor in itself as a contraindication to radium. The cervical, the submucous and the pedunculated varieties of fibromyoma are not suitable for radium treatment. Fibroids undergoing degeneration should not be treated with radium.

The chief positive indication for radium treatment is uterine hemor-

rhage due to the fibromyoma. Radium may be used, however, when hemorrhage is absent. The results of treatment are, in most cases, the cessation of the menorrhagia and metrorrhagia and the production of amenorrhea; the reduction of the size of the fibroid, which may in some instances disappear. In some cases, the menses may reappear even after as long a period as two years. The application of radium entails no operative mortality. If radium fails, operation can be resorted to if thought advisable.

Technic of Treatment of Uterine Fibroids.—The technic of treatment naturally varies, depending upon the nature of the case and also upon the operator. Radium may be applied either by intrauterine applications, or externally by surface radiations over the abdomen when the size of the fibroid warrants the latter procedure. Good results may be obtained by moderate doses in the uterus. In cases in which radium is applied externally over the abdomen large doses are necessary. The intrauterine application of radium is to be preferred as a rule to its external application. Both procedures may be used coincidently in suitable cases. In some cases, when there is great objection to intrauterine application or when the pelvis is choked by the growth and intrauterine manipulation is impossible, radium may be introduced into the posterior fornix and at the same time powerful radiations may be used over the fundus uteri. The latter method has been used successfully by Hayward Pinch and others. External treatment alone may be successful.

1. **Intrauterine Radiations.**—By an intrauterine application of sufficient intensity the endometrium may be destroyed but ovarian activity may be preserved. In this respect the intrauterine application of radium appears to possess features of advantage over treatment with x-rays, as the symptoms of the menopause are frequently slight when radium is used in this manner and may be pronounced after x-ray treatment. The amenorrhea that is produced should last if possible until the fibroid has practically disappeared as the tumor may begin to grow again if menstruation returns. If this latter event happens, the treatment may be repeated if thought advisable. The production of amenorrhea requires ordinarily an application to the interior of the uterus of from 1000 to 1500 millicurie hours. The quantity of radium used and, therefore, the length of the application vary with different operators.

Dr. Howard Kelly has used 500 millicuries in the uterus for three hours. In the technic of the above author's treatment, the radium tube, screened to emit only gamma rays was screwed to the end of an ordinary uterine sound and introduced to the fundus uteri. The radium was allowed to remain not longer than one-half hour in one place, an average of six changes being made by turning once from right to left and then by withdrawing the sound one cm. at a time.

Dr. J. G. Clark has used 50 milligrams enclosed in one or two tubes. An intrauterine exposure of from six to twenty-four hours has been

given by this author, the shorter exposure being used in women under thirty-five and the longer, in women in the menopausal cycle.

Hayward Pinch of the London Radium Institute has applied about 50 millicuries screened with 2 millimeters of lead to the posterior fornix or to the interior of the uterus. The same quantity was used simultaneously over the fundus. When the posterior fornix was the site of application, a total exposure of thirty to sixty hours was given in the course of five to ten days. The series of treatments was repeated in six to eight weeks. If the interior of the uterus was treated, an exposure of from twenty-four to thirty hours was given.

My method consists frequently in the use of 100 millicuries properly distributed over the interior of the uterus. The screening is usually 2 millimeters of brass or its equivalent of another metal plus 2 millimeters of rubber. With or without gas anesthesia, the cervix is dilated and curettage is performed in order to exclude malignancy and remove any polypi. The cavity of the uterus may be swabbed lightly with a 5 per cent solution of iodine. The radium tube or series of tubes, arranged so as to radiate the uterine cavity homogeneously, is then introduced and allowed to remain for from ten to fifteen hours. As a result of an intrauterine treatment, there may be some nausea and vomiting and a feeling of depression in the ensuing twenty-four or forty-eight hours. There is usually no subsequent pain. Hemorrhage usually stops at once, but in some cases may diminish gradually and may persist to a slight degree for several weeks.

Following the treatment there may be a yellowish leucorrhea but this usually ceases within six weeks. The menopausal symptoms naturally vary with the age of the patient. In younger patients they may occasionally be quite severe, but in those within or past the menopausal cycle, sequelae of this kind are slight or absent.

2. **Surface Radiations.**—By employing surface radiations over the abdomen a result similar to that obtained by intrauterine applications may be produced. Surface radiations are adapted to very large tumors.

Employing this method, Kelly has used 1000 millicuries at a distance of 10 centimeters from the skin. The emanation was distributed at various points over the abdominal tumor and a total exposure of twenty-four hours was given. A satisfactory result may be obtained by using 500 millicuries, screened with 2 millimeters of brass. Distributed on a pad so that there may be a concentration of 5 millicuries per square centimeter, 500 millicuries may be applied to different areas at a distance of 6 centimeters from the skin for twenty-five hours over each area in periods of ten or more hours each. At a distance of 10 centimeters, 500 millicuries may be applied for thirty-six hours in several periods. The course of treatment should extend over one or two weeks and may be repeated in six or more weeks if thought desirable,

although smaller doses should invariably be given in subsequent treatments.

C. METRITIS AND ENDOMETRITIS

In chronic metritis and endometritis recovery may often be brought about by the intrauterine application of radium. Several tubes, arranged tandem and containing a total of 50 millicuries, screened with the equivalent of one millimeter of lead and one millimeter of rubber, may be applied for from eight to ten hours. The treatment may be repeated in six weeks if necessary. Endometritis that has resisted all the ordinary measures and was formerly curable only by the removal of the uterus is sometimes completely relieved.

D. METRORRHAGIA AND MENORRHAGIA NOT DUE TO CANCER OF FIBROID

In metrorrhagia and menorrhagia due to causes other than cancer and fibroid, radium is sometimes of the greatest value. S. M. D. Clark has reported 50 cases of the above conditions benefited by radium. This author states that in "hemorrhage in young women" without definite etiology, in aggravated and intractable dysmenorrhea, and in "chronic metritis" with bleeding, radium has given promise of complete relief.

E. MYOPATHIC HEMORRHAGE

In myopathic bleeding from the uterus many authors have reported favorable results. In such cases, in which there is persistent uterine bleeding at the menopause without gross demonstrable cause, radium is very efficient. One hundred millicuries screened with one millimeter of silver and two millimeters of rubber may be applied to the uterine cavity for ten hours.

CHAPTER XVII

RADIUM IN DERMATOLOGY

We have already referred to the fact that radium rays may produce either a "selective" or an "inflammatory" reaction in the skin. By some writers, the "selective reaction," a process by which pathologic tissues are altered without visible inflammatory changes, is held to be the more important. The ease, however, with which the actual destruction of certain pathologic tissues can be produced leads us to place radium in the front rank as a destructive agent. Within certain limits, radium is superior to the other common destructive agents used in dermatology, such as chemical caustics, the cautery, carbon dioxide snow or liquid air, electrolysis, etc. In actual dermatologic practice, one often combines the effect of the "selective" and the "inflammatory" reaction. The inflammatory reaction should be reduced to a minimum, however, and, if possible, avoided altogether in treating most dermatoses. Too free use of the inflammatory reaction, when the cosmetic appearance of the treated area is important, is undesirable on account of the possible development, within the succeeding eight or ten months, of telangiectases. These are almost always the result of too large doses.

Fortunately even a scar resulting from too strong doses of radium is almost always smooth, elastic and free from defects inherent in almost every other kind of destructive measure, except the telangiectasia mentioned above. In favorable cases, the color of the previously irradiated skin area is almost like that of normal skin. A slight pigmentation may be present for a time, but this always disappears sooner or later. "From the histologic point of view, the action of radium on the integument, at least in therapeutic applications, can be shown to produce the same effects whether the condition of the skin be normal or diseased. The elements of the epidermis, whether physiologic or pathologic, are absorbed by degrees and disappear, while the overlying malpighian epithelium persists. The cells of the vascular connective tissue, whether normal or modified by inflammation or a carcinomatous process, have an alternating evolution. In the first stage, they return to the state of embryonic connective tissue cells; in the second, they again arrive at maturity under the form of elongated fibroblasts, which are superimposed and follow the regular lines of stratification, again forming connective tissue bundles and elastic fibers." (Dominici and Barcat.)

We may mention here the main groups of dermatoses in which radium offers a possibility of use:

A. Malignant tumors.
B. Benign tumors.
C. Chronic infections.
D. Inflammatory and granulomatous infiltrations of uncertain nature.
E. Hypertrophies.
F. Neuroses.
G. Disorders of the appendages of the skin: (a) Sebaceous glands; (b) hair and hair follicles.

A. MALIGNANT TUMORS

The treatment of epithelioma, carcinoma, and sarcoma of the skin has already been referred to in the chapter on radium in general surgery. Among the other malignant growths of the skin which may be greatly benefited by radium are Paget's disease, xeroderma pigmentosum, and mycosis fungoides.

B. BENIGN TUMORS

(a) Keloids

Keloids and certain cicatricial bands are very favorably influenced by radium.

In keloids of recent formation, especially when they occur in chil-

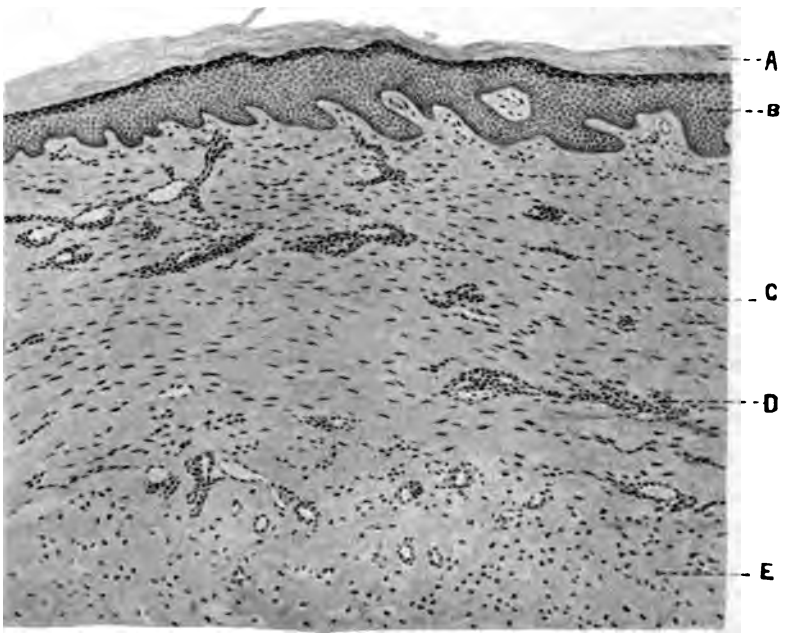

Fig. 102.—Cicatricial keloid, following a burn of the face. Before radiation. Slightly enlarged. The connective tissue cells are scanty and the elastic fibers even more so.

A, Horny layer. *B*, Thinned rete mucosum. *C*, Keloidal tissue with elements arranged parallel to the plane of the section. *D*, Capillaries surrounded by a zone of cells. *E*, Deeper portions of the keloidal fibroma arranged perpendicularly to the plane of the section.

dren, a very excellent result is frequently obtained. In some cases the skin may be quite normal in appearance after involution of the keloid. In other cases, the treated area may be too white or too red, or it may have a smooth, glazed appearance which, although differing from normal skin, is not unsatisfactory when compared with the keloid itself. Usually the keloid is levelled and pain is completely relieved. Compared with other methods of treatment, radium is easily the method of choice in the treatment of this condition.

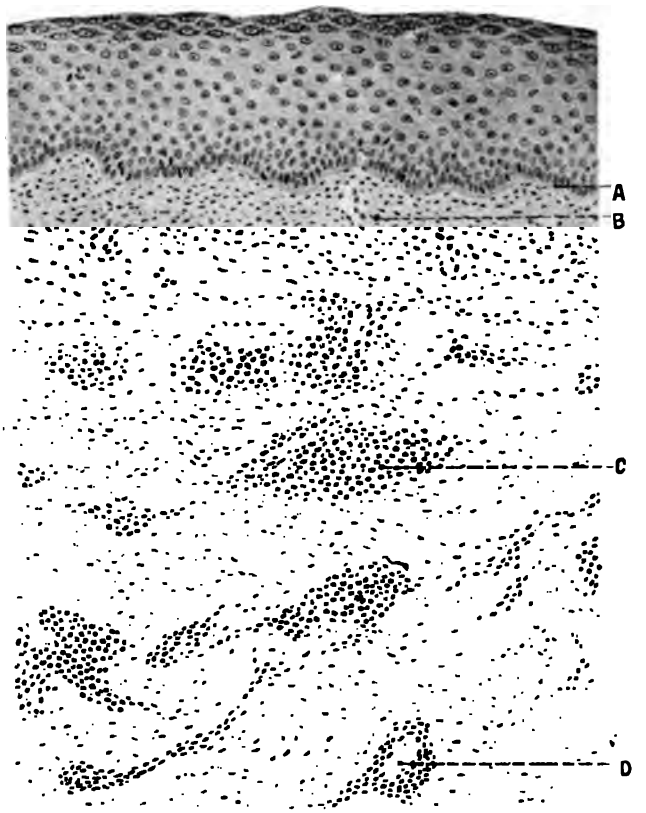

Fig. 103.—Same keloid as in Fig. 102 after radiation. Highly magnified. Greater development of the connective tissue cells; polymorphism of these cells; notable increase of elastic fibers. *A*, Epidermis directly above corium in a state of transformation. *B* Surface zone of the keloid transformed into young fibroma, rich in cells. *C*, Young fibroblasts forming a zone resembling a myomatous development. *D*, Deeper zone which has undergone less advanced changes.

In keloids mixed with scar tissue, the prognosis is not so favorable as more intensive treatment must be given.

The Technic of Treatment of Keloids.– The technic of treatment of true keloids will vary greatly according to the age of the patient and the size and duration of the lesion. A tentative course of treatment may first be given. One-fourth or one-half strength varnish or glazed applicators may be used. Screened with $\frac{1}{10}$ mm. of lead and applied closely to the skin, a course of two to four hours in six periods may be

given. At a distance of 2 mm., the time may be doubled. In children one-half or one-fourth of this dose should be used. In keloids of considerable thickness, radium salts or emanation in tubes instead of varnish plaques may be used advantageously. One hundred millicuries of radium

Fig. 104.—Keloid of right great toe. Photograph taken May, 1914. Patient referred by Dr. J. R. Buchbinder.

Fig. 105.—Patient in Fig. 104 after radium treatment. Photograph taken January, 1915.

emanation having a concentration of 5 millicuries per square centimeter, screened with 1 millimeter of lead and at a distance of 1 centimeter may be applied for eight or ten hours in periods of one or two hours each. The series of treatment may be repeated in about six weeks, but the subsequent course should be of less intensity.

"Above all, the principle which governs the technic, and of which the operator must never lose sight, is the necessity for influencing the keloids to the extreme depth of their base, and acting on their peripheral prolongations, which sometimes extend far beyond their visible limits. The treatment of a keloid should only be considered complete when the tissues show an almost normal elasticity on palpation, even at a depth.

"It is possible then, to make use of total radiations of great power, composed largely of Beta rays, and employ them in frequently repeated exposures of short duration; or of 'surpénétrant' radiations of weak quantitative value, allowing them a sufficiently long action; or of the simultaneous application of several instruments acting opposite each other, by the system of 'cross fire.' By these means, which lead to the absorption of the growths, we can utilize the selective power of radium. But they are sometimes slow, and in order to gain time it is often well to act more energetically, undeterred by the fear of producing a certain degree of destructive inflammation. In the application of these different processes, two important data must be borne in mind, viz., (1) the great resistance shown by keloidal tissue, from which results the possibility of using fairly large doses, without producing any reaction worth mentioning; (2) the futility of aiming at the entire avoidance of superficial inflammation. If the 'specific' dose be slightly exceeded, a small dry crust with a dry base is produced which will not in any way hinder the course of the treatment. If there is any hesitation as to which of two doses, intended to obtain simple modification without destruction, shall be chosen, there can, therefore, be no objection to deciding on the stronger. Keloids which respond most readily to the employment of specific doses are those of recent formation in process of evolution, and those of young children." (Wickham and Degrais.)

In the treatment of keloids mixed with scar tissue and also in dealing with fibrosclerotic bands, the doses suggested above may be slightly increased so as to cause an actual destructive reaction. This procedure should be followed, however, only when the milder doses have failed. It must be remembered also that destructive doses may cause a reaction requiring weeks for healing and that telangiectasia may eventually occur. Even under these circumstances the final result, skillfully produced, is usually much to be preferred to the original lesion. As pointed out by Wickham and Degrais not all disfiguring scars are amenable to radium treatment. Depressed scars, e.g., such as those resulting from smallpox, cannot be remedied by radium.

Fig. 106.—Keloid of back due to burn from a flat iron. The tumor was situated between the spine and lower angle of right scapula. Photograph taken April, 1914.

Fig. 107.—Patient in Fig. 106 after radium treatment. Photograph taken September, 1914. Only the lower portion of the keloid had been treated when the photograph was taken. Later the rest of the tumor was removed with radium.

Fig. 108.—Keloid of back of neck. Recurrence after surgical removal. Patient referred by Dr. Bayard Holmes.

Fig. 109.—Patient in Fig. 108 after radium treatment.

Fig. 110.—"Acne keloid" of back of neck.

Fig. 111.—Patient in Fig. 110 after radium treatment.

Fig. 112.—Keloid of face following a burn. Patient referred by Dr. T. R. Hinchion. Photograph taken January, 1919.

Fig. 113.—Patient in Fig. 112 after radium treatment. Photograph taken June, 1920.

(b) **Angiomata and Lymphangiomata**

Angiomata and lymphangiomata, as a class, were most unsatisfactory to treat until the advent of radium. Many of the more modern methods, such as the injection of boiling water or hydrogen peroxide, destruction by liquid air, CO_2 snow, electrolysis, etc., are more or less painful and on this account alone are unsatisfactory, particularly in the treatment of children. With these destructive methods, it is difficult or impossible,

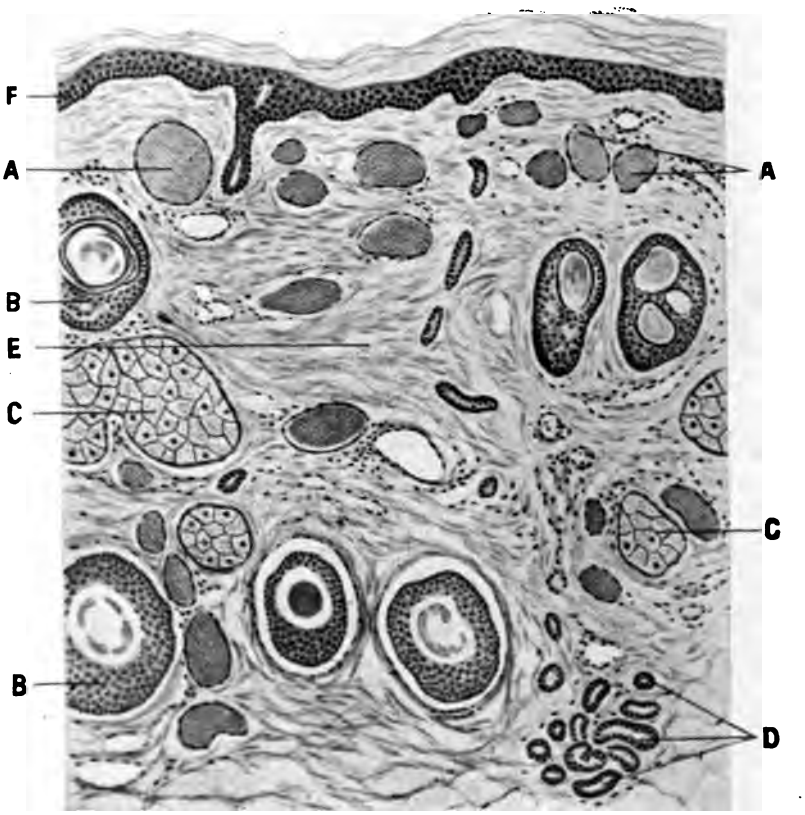

Fig. 114.—Flat angioma of the hairy surface. Before radiation. Slightly enlarged (97 diameters). *A*, Capillaries of flat endothelium filled with blood elements. *B*, Hairs, perpendicular section. *C*, Sebaceous glands. *D*, Sudoriparous glands. *E*, Corium rich in collagen, poor in cellular elements. *F*, Normal epidermis.

in extensive cases, to obtain uniformity of coloring of the affected areas. With radium, on the other hand, a fading rather than a destruction of the angioma can often be brought about. While a certain place is left for other methods, radium is our most satisfactory agent in dealing with most cases of angiomata and lymphangiomata. Not all cases respond equally well, but in favorable and selected cases a good cosmetic result may be anticipated.

In considering the treatment of angiomata with radium from a clin-

ical standpoint, we may follow, in the main, the grouping suggested by Wickham and Degrais. On the basis of treatment, these authors have divided vascular nevi into the following groups:

1. Flat, superficial angiomata, level with the skin.
2. Flat, deeply infiltrating angiomata, level with the skin.

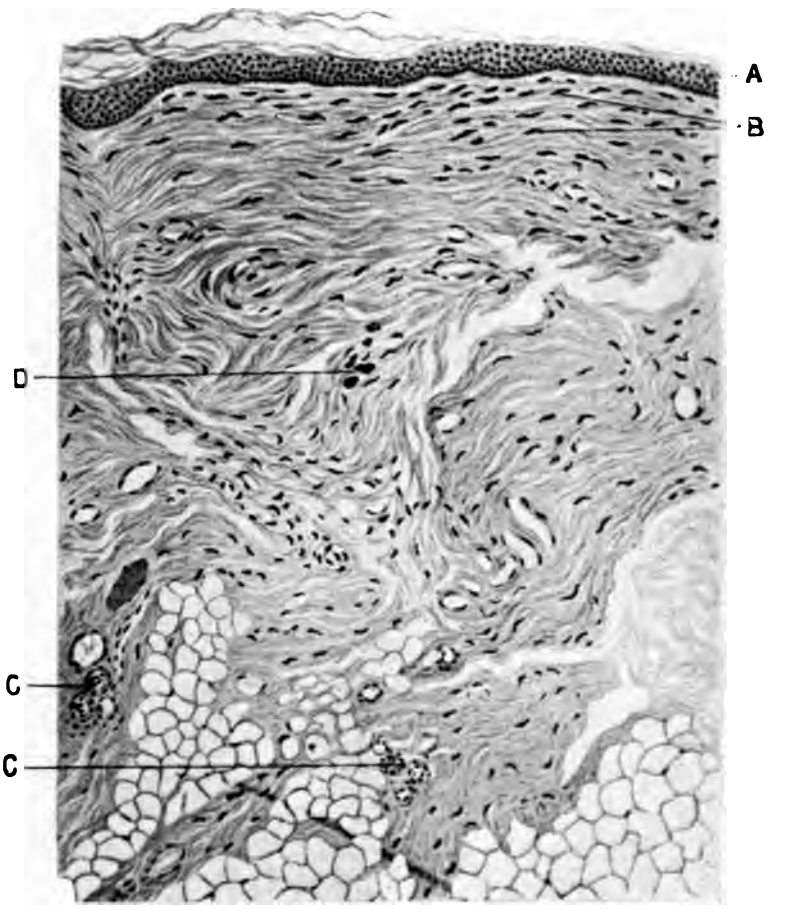

Fig. 115.—Same angioma as in Fig. 114, after treatment with radium by the method of "selective reaction," i.e., without visible macroscopic inflammation. Slightly enlarged (120 diameters). The epidermis is of normal thickness and freed from interpapillary encroachments. The derma is composed of connective tissue rich in cells of mature fibroblast type, which are arranged parallel to the epidermis. The connective tissue and elastic fibers have a uniformly regular arrangement, vessels are scanty, hairs and follicles have disappeared, only traces of sudoriparous glands.

A, Epidermis resting on basal tissue which is hardly recognizable. *B*, Zone below the epidermis, where the cells are abundant and parallel to each other and to the epidermis. *CC*, Traces of sudoriparous glands. *D*, Star-shaped connective tissue cells which have not yet evolved into mature fibroblasts.

3. Raised angiomata, usually with hard and more or less sclerotic surface.
4. Raised angiomata, usually soft and sometimes pulsatile and erectile.
5. Deep, subcutaneous and submucous angiomatous tumors.

The above groups include the more common types of angiomata. These

Fig. 117.—Patient in Fig. 116 after radium treatment.

Fig. 116.—Cavernous angioma of tip of nose.

Fig. 119.—Patient in Fig. 118 after radium treatment. Photograph taken September, 1918.

Fig. 118.—Cavernous angioma of forehead. Photograph taken March, 1918.

Fig. 117.—Patient in Fig. 116 after radium treatment.

Fig. 116.—Cavernous angioma of tip of nose.

Fig. 119.—Patient in Fig. 118 after radium treatment. Photograph taken September, 1918.

Fig. 118.—Cavernous angioma of forehead. Photograph taken March, 1918.

Fig. 120.—Cavernous angioma of lower lip. Patient referred by Dr. S. L. Fridus.

Fig. 121.—Patient in Fig. 120 after radium treatment.

Fig. 122.—Flat angioma of side of face, neck, chin and lower lip.

Fig. 123.—Patient in Fig. 122 after radium treatment. The result in this case was better than indicated by the photograph. The angioma was removed by "selective reaction."

Fig. 124.—Vascular nevus of face and neck. This angioma was elevated, deeply infiltrated, and of a dark red color. Photograph taken July, 1914.

Fig. 125.—Patient in Fig. 124 after radium treatment. The small area on the neck had not been treated when the photograph was taken (July, 1915). The result in this case is not so good as it appears in the photograph as the treated areas are a little too white and the coloring is not quite uniform.

Fig. 126.—Angioma of side of face and head in patient aged six weeks. Lesion appeared on nose when patient was one week old and was spreading when treatment was begun. Photograph taken September, 1914. Patient referred by Dr. David Lieberthal.

Fig. 127.—Patient in Fig. 126 at age of one and one-half years, after radium treatment. Photograph taken March, 1916. The result in this case was fully as good as it appears in the photograph.

Fig. 128.—Slightly elevated angioma of side of face. Lesion was of dark, purplish-red color. Patient referred by Dr. H. Edward Sauer.

Fig. 129.—Patient in Fig. 128 after radium treatment. The result in this case is not as good as indicated in the photograph as a few telangiectases have appeared in the last year. These are easily concealed, however.

Fig. 130.--Angiosarcoma (?) of left arm; note tumor of arm and flat angioma of back of arm. Photograph taken April, 1916.

Fig. 131.—Patient in Fig. 130 after radium treatment. Note the disappearance of tumor and normal outline of arm. Method of dressing with strips of rubber tissue. A superficial dermatitis is also shown. Photograph taken June, 1916. Patient was well five years later.

Fig. 132.—Large cutaneous and subcutaneous angioma of left side of neck in child aged 6 months. Photograph taken October, 1918.

Fig. 133.—Patient in Fig. 132 after radium treatment. Nevus disappeared without inflammatory reaction. Photograph taken May, 1919.

different types, however, merge into each other and different forms may be present in the same person.

The Technic of Treatment of Angiomata.—The method of treatment with radium naturally varies with the type. For most superficial angiomata, nothing equals the "toiles" or the glazed plaques. For deep angiomatous tumors, tubes may be employed, although the flat applicators answer equally as well.

1. *Flat Superficial Angiomata ("Port-wine Stains").*—In the treatment of this type of tumor, one cannot too strongly insist upon the necessity of the avoidance of inflammatory reaction. The production of slight redness and scaling of the skin is sometimes permissible, but an endeavor to bring about more rapid results by strong treatment will only be fraught with disaster. If the dosage is too powerful or the technic unskillful, the coloring may not be uniform and telangiectasia may occur. As an example of the technic, we may suggest the use of a $\frac{1}{20}$ strength "toile." With this style of applicator screened with $\frac{1}{100}$ or $\frac{1}{50}$ mm. of aluminum and applied closely to the skin, an exposure of from two to four hours in periods of an hour each on successive or alternate days will suffice. In children, one-half of the above dose should be given. If a slight fading of the angioma occurs in six or seven weeks, sufficient will have been accomplished. Subsequent series of treatments should be of less intensity. With no class of cases is a refined and skillful technic more necessary in order to accomplish good results. Sometimes only a partial fading of the angioma can be brought about.

2. *Flat, Deeply Infiltrating Angiomata.*—The method of treatment of this type of angioma is similar to that employed in the first group, except that it is permissible to use stronger doses. Angiomata of the first group can sometimes be quite well concealed by the artifices of the toilet. Angiomata of the group that we are now considering are often so deeply colored and unsightly that no amount of artificial coloring or disguising really conceals them. We are justified, therefore, in proceeding somewhat more boldly. With the same apparatus and screen used in treating tumors of the first group, we may give an exposure of five hours in periods of an hour each on successive days. With one-fourth strength apparatus, screened with one-tenth millimeter of lead and applied closely to the skin we may give a total exposure of from three to four hours. At a distance of 2 millimeters, six or eight hours may be given. Only a few square centimeters should be treated at one time until the effect is observed. Severe reactions should be avoided. In subsequent courses of treatment, instituted after six weeks or two months have elapsed, the screening may be increased to $\frac{2}{10}$ mm. of lead and a total exposure of five or six hours in several periods of one or two hours each may be given. It is difficult to obtain good results in this group, but in some cases the final appearance is excellent.

3. *Raised "Hard" Angiomata.*—This group comprises a considerable number of clinical types with no exact limitations. The size and extent of the tumors vary greatly. In some, the surface may be smooth; in others papillated and irregular. A varying degree of hardness is noted on palpation, some being quite sclerotic. In this group, one is justified in producing definite reaction. With ¼ strength applicators, applied closely to the skin, a total exposure of two hours when unscreened, or five hours when screened with $\frac{1}{10}$ mm. of lead may be given as a first course. Screened with $\frac{1}{10}$ mm. of lead plus 2 mm. of rubber, ten hours may be given. Not over 4 square cm. should be treated at one time. The treatment should be divided into several periods of one hour each. When the reaction subsides, a less intensive course with double the thickness of screen may be given.

4. *Raised, "Soft" Angiomata.*—In this group are included variously sized tumors. A frequent type is the "cavernous angioma," seen particularly in infants. This tumor is elevated one or more centimeters above the skin level, and is frequently limited to an area of several square centimeters. In more extensive cases, the entire side of the head may be involved so that there is great deformity. It is in this group that radium is particularly satisfactory in its effects. One should endeavor to utilize to the fullest extent the selective action of radium. Success frequently attends doses that produce little or no inflammatory reaction. The "cross fire" method suggested by Wickham, in which the raised tumor is attacked from different sides, is especially useful. With one-quarter strength applicators, screened with one-tenth millimeter of lead and applied closely to the skin, an exposure of three or four hours in several periods may be given on one area. At a distance of 2 millimeters, eight hours may be given. As in the previous instances, not over 4 square cm. should be treated until the effect is observed. The course may be repeated in six or eight weeks. In the case of very extensive tumors in infants, an exposure of two hours when the applicator is closely applied may be sufficient for the first course of treatment. Subsequent courses should be of less intensity.

5. *Deep, Subcutaneous and Submucous Tumors.*—Very extensive tumors may be treated successfully. In these cases the deep penetrating method should be used. It is best to treat separate sections of the tumor successively so as not to give an overdosage. Tubes may be used in this type of tumor, although plaques are more satisfactory. One hundred and fifty millicuries of radium emanation, having a concentration of 5 millicuries per square centimeter, screened with 2 millimeters of brass and placed at a distance of two centimeters, may be used on an area of about 30 square centimeters for ten hours in several periods of two or three hours each. Full-strength radium plaques may be used in a similar manner.

The "cross fire" method should be utilized to the utmost in order to spare the skin. At intervals of six or eight weeks, subsequent courses of less intensity may be needed, although two, or at most three, courses are

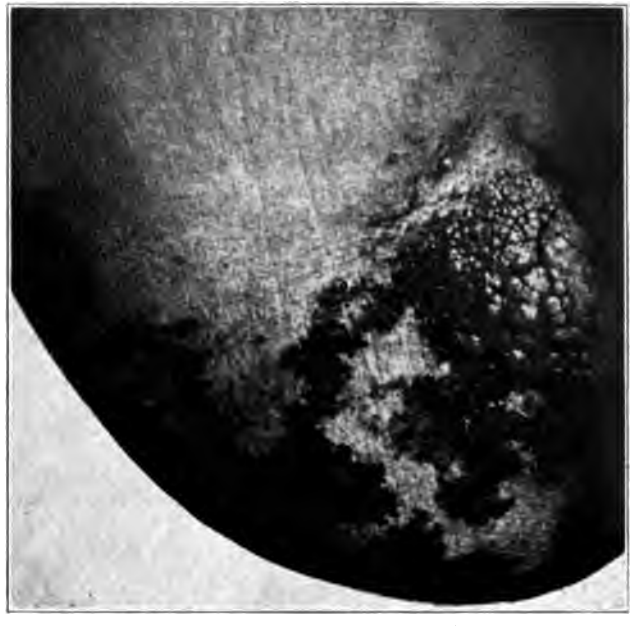

Fig. 134.—Lymphangioma circumscriptum of right buttock and inner surface of right thigh. Photograph taken April, 1914. Patient in lithotomy position.

Fig. 135.—Patient in Fig. 134 after radium treatment. Photograph taken December, 1915. A recurrence took place six years later which again yielded to radium.

Fig. 136.—Pigmented nevus of left lower eyelid and face.

Fig. 137.—Patient in Fig. 136 after radium treatment.

Fig. 139.—Patient in Fig. 138 after radium treatment.

Fig. 138.—Pigmented hairy nevus of left eyebrow and forehead.

Fig. 140.—Linear nevus in patient aged 4 years. Black, wart-like growths were present on nose, lip, chin and cheek. The side of the face was of a tawny yellow color. The soft and hard palates were also involved. Photograph taken January, 1915. Patient referred by Dr. F. A. Besley.

Fig. 141.—Patient in Fig. 140 after radium treatment. Photograph taken July, 1915. Treatment not quite completed.

usually sufficient. Oftentimes, large angiomatous tumors may be made to disappear without inflammatory reaction, the overlying skin being scarcely or not at all affected unfavorably. The writer has treated with

Fig. 142.—Tuberculosis verrucosa cutis of first phalanx of left middle finger.

Fig. 143.—Patient in Fig. 142 after radium treatment.

radium more than three hundred angiomata of various types. In some cases, the results have been excellent. In a few cases, there has been no noteworthy improvement.

The Technic of Treatment of Lymphangiomata.—These rare tumors yield in excellent fashion to radium. Abbe reported upon the treatment of the first cases in 1915 and a few months later I reported an extensive case involving the buttock and thigh that had been successfully treated. In lymphangiomata affecting the mucous membranes and particularly

Fig. 144.—Tuberculosis verrucosa cutis of first phalanx of left thumb.

Fig. 145.—Patient in Fig. 144 after radium treatment.

the tongue, radium is of unique value and can hardly be replaced by any other agent. The method of treatment is similar to that for angiomata of the third group.

(e) Nevus Pigmentosus

Pigmented nevi involving an area of several square centimeters are amenable to radium. Very minute nevi should be treated by other meth-

ods. Growths that are very unsightly in consequence of rugosities and great thickening, the presence of hair, and very dark pigment, are especially likely to yield to treatment. Radium has unfortunately no selective action on pigmented nevi and in order to cause them to disappear destructive doses must be used. The final result therefore may not be as good as in angiomata, due to the fact that the treated area may be

Fig. 146.—Lupus vulgaris of right cheek in girl aged 13.

unevenly colored and there may be points of repigmentation. We do not therefore recommend the use of radium in faintly pigmented nevi.

The Technic of Treatment of Pigmented Nevi.—Great care should be used in the treatment in order not to give excessive doses. With one-quarter strength applicators, applied closely, an exposure of one or two hours may be given without screening. Following this, an exposure of two hours with a screen of $\frac{1}{10}$ millimeter of lead may be given. This

procedure produces a slightly destructive action. The treatment may be repeated, but with less intensity, in eight weeks. The final result will depend very largely upon the judicious selection of cases and perhaps most of all, as in other cosmetic difficulties, upon the skill and care with which the treatment is carried out.

"Fordyce's disease" of the mucous membrane of the cheek and lips

Fig. 147.—Patient in Fig. 146 after radium treatment.

has been treated successfully by Hayward Pinch, myself and other writers. A glazed plaque of ¼ strength, unscreened, may be used and a sharp reaction may be produced. An exposure of forty-five to sixty minutes may be given and repeated, if necessary, in a few weeks.

In various other benign tumors of the skin, radium has been found to be of value. Among these may be mentioned especially linear nevus, in which radium is of the greatest value. Dermatitis papillaris capillitii, molluscum

Fig. 148.—Lupus vulgaris of right cheek.

contagiosum, multiple benign cystic epithelioma and some types of xanthoma are also susceptible to radium.

C. CHRONIC INFECTIONS

(a) Tuberculosis

In certain types of skin tuberculosis, radium is of value. Tuberculosis verrucosa cutis frequently responds well. Destructive doses, such as may

Fig. 149.—Patient in Fig. 148 after radium treatment.

be obtained by using ¼ strength applicators with a screen of 1/10 mm. of lead for five or six hours in several periods of one to two hours each, may be used. In lupus vulgaris, radium is only of limited use, being, in the writer's judgment, distinctly inferior to the Finsen light. In using radium, the best plan of procedure consists in using ¼ or ½ strength glazed applicators with a 1/10 mm. lead screen. A total exposure of six to twelve hours may be given in divided doses. Only small lesions should ordinarily be

treated. Large lupus patches may even spread at the border and become worse under radium treatment if insufficient doses or unskillful technic are used. It is the general experience that radium has practically no selective action on lupus tissue. In lupus vulgaris of the mucous membranes, radium often has a very beneficial effect. Doses of less intensity than those used for the skin should be employed.

(b) Blastomycosis

In 1913, the writer reported the results of the radium treatment of blastomycosis of the eyelid. Since that time, several other cases of blastomycosis of the skin have been treated successfully. Radiation similar to that

Fig. 150.—Blastomycosis of left inner canthus

Fig. 151.—Patient in Fig. 150 after radium treatment.

used for tuberculosis, but of less intensity is efficient. Degrais, Wickham and others have found local radium treatment of value in aiding resolution of syphilitic skin eruptions. The technic is similar to that described above as suitable in tuberculosis.

Radium has been used successfully by Kahler, Guttman and others in rhinoscleroma and by Heyerdahl in actinomycosis.

D. INFLAMMATORY AND GRANULOMATOUS INFILTRATIONS OF UNCERTAIN NATURE

In this group of dermatoses, radium is of considerable value. In psoriasis, lichen planus, lichen chronicus simplex, chronic eczema and

Fig. 152.—Lupus erythematosus of nose and cheeks.

Fig. 153.—Patient in Fig. 152 after radium treatment. Photograph taken two months after treatment.

lupus erythematosus, radium treatment offers, in selected cases, a great amount of relief.

In psoriasis of the nails, radium is particularly useful. In obstinate patches of psoriasis that do not yield to ordinary measures radium may be used successfully. It must be remembered, however, that neither radium nor any other measure prevents recurrence of the patches. With

Fig. 154.—Lupus erythematosus involving nose and cheeks.

¼ strength applicators, screened with $\frac{1}{10}$ mm. of lead, an exposure of one or two hours and often less, in several periods, is usually sufficient to cause involution. Inflammatory reaction should be avoided.

In lichen planus confined to small areas radium often relieves the itching and hastens involution. In lichen planus of the mucous membranes, radium is especially valuable. The technic of treatment is the same as that suggested for psoriasis. Not more than ¼ of the dose employed on the skin should be used on lesions of the mucous membranes.

In lichen chronicus simplex, radium often gives the most striking relief, the itching frequently disappearing very promptly. Short applications of ¼ to ½ strength glazed applicators, unscreened, are advisable. Two or three exposures, each lasting three minutes, and repeated at intervals of a week, are efficient. Inflammatory reaction should be avoided.

Certain cases of chronic eczema may yield to similar treatment.

The writer has treated more than 50 cases of lupus erythematosus

Fig. 155.—Patient in Fig. 154 after radium treatment.

with radium. In this curious and puzzling disease, radium is one of our most valuable agents. Considerable judgment is necessary in treating this disorder, and caution should be practiced until the degree of irritability of the individual case is made evident. Most cases require only a moderate reaction to produce evolution. Treatment may be carried out by employing ¼ strength glazed applicators, screened with $\frac{1}{10}$ mm. of lead. One-half hour exposures may be given on successive or alternate days until four or five treatments have been given. The

Fig. 156.—Lupus erythematosus involving right cheek and upper lip.

Fig. 157.—Patient in Fig. 156 after radium treatment.

Fig. 158.—Lupus erythematosus of four years' duration.

Fig. 159.—Patient in Fig. 158 after radium treatment. Involuted areas show the scarring of the disease and are of a lighter color than the normal skin.

effect is noted and the treatment is repeated as soon as the reaction, which may last for from two to four weeks, has subsided. Care must be taken that the edge of the applicator overlaps for at least five to ten millimeters, the visible edge of the disease. This treatment is usually adapted only to the cases of "fixed type." Freedom from the disease for several years may be experienced in certain cases. In other cases, a relapse may occur in a few months, or even sooner. In some cases of lupus erythematosus, little benefit is derived from the treatment. In leukemia cutis, radium is of value and may cause resolution of the involved areas.

E. HYPERTROPHIES

In many of the disorders classed as hypertrophies, radium is of considerable value. In clavus, callositas, and the various keratoses, such as keratosis senilis, x-ray keratosis, angiokeratoma, etc., radium is of value. The general method of treatment of these disorders consists in the use of ¼ strength apparatus, unscreened, for one-half to two hours, or screened with $\frac{1}{10}$ mm. of lead for three to four hours.

Warts and Papillomata

Although often regarded as trivial, the subungual and periungual wart, and the palmar and plantar wart deserve special mention because they are peculiarly resistant to the ordinary dermatologic measures. The plantar wart may cause great distress and pain on walking. As a rule, all these growths yield easily to radium treatment. One-fourth strength glazed apparatus unscreened applied carefully for from one-half to two hours is usually sufficient to cause involution. A still better method in some cases, because the reaction produced is negligible, consists in using the same apparatus, screened with $\frac{1}{10}$ mm. of lead, for four hours in periods of one hour each. In certain rare disorders, such as acanthosis nigricans and Darier's disease, radium treatment would undoubtedly be of value insofar as the removal of localized areas of the disorder is concerned. R. L. Sutton has used radium successfully in a "synovial lesion" of the skin.

F. NEUROSES OF THE SKIN

We have already spoken of the relief obtained by the use of radium in certain itching dermatoses, notably lichen chronicus simplex, lichen planus, and eczema. There are other disorders classed as neuroses in which the subjective symptoms are prominent, but in which little or nothing is seen objectively except the lesions produced by scratching. Localized pruritus, such as pruritus ani and pruritus vulvae, is frequently relieved by radium. In these affections, the best method of treatment is by means of unscreened glazed apparatus. Exposures of

three to five minutes' duration repeated several times at intervals of a week, may be given. The total amount of radiation should never be sufficient to produce an inflammatory reaction. In various other affections, the analgesic action of radium has been made use of. In hyperesthesia, following herpes zoster, in neuritis and in intercostal and sciatic neuralgia, Wickham found radium of value. He used approximately ¼ strength apparatus screened with $\frac{1}{10}$ mm. of aluminum and gave applications of from ten to fifty minutes. Reaction in the skin should be avoided in this class of cases.

G. DISORDERS OF THE APPENDAGES OF THE SKIN

(a) The Sebaceous and Sweat Glands

In selected cases of acne rosacea radium is of value. In rhinophyma very good results have been obtained by Wickham and Degrais and others. In these cases, ¼ strength glazed applicators, screened with $\frac{1}{10}$ mm. of lead, are usually employed and a slight reaction may be produced. A total exposure of two or three hours in several periods will usually be sufficient. Subsequent courses may be given at intervals of three to six weeks. Good results may follow the local treatment of acne varioliformis although, of course, no influence is exerted in preventing the formation of new lesions. In hyperidrosis, radium is sometimes of value. The glazed plaques are the most convenient form of apparatus. Inflammatory reaction should never be produced.

(b) Hair and Hair Follicles

In the extreme cases of hypertrichosis which may cause so much mental anguish as to wreck the happiness of the individual, radium may occasionally be employed. Sometimes, however, in order to produce permanent alopecia a degree of atrophy must be produced that is undesirable. Telangiectasia may also be caused. In selected cases, however, we have obtained very excellent results. In hypertrichosis, the following technic may be used. All areas that are not to be affected must be covered by at least 5 mm. of rubber covered lead. One hundred fifty mc., screened with 2 mm. of brass, may be arranged on a wooden pad 6x8x2 cm. At a distance of 2 cm., which is the thickness of the wooden pad, an exposure of thirty hours in two periods may be given. In cases in which temporary alopecia is desired, as in ringworm and sycosis vulgaris, radium may be used instead of x-rays, though often inferior in convenience to the latter agent. Radium is perhaps safer in inexpert hands. In extensive ringworm of the scalp, we have used the following technic. Blocks of soft wood or cork (2x2x1 cm.) may be arranged to form an applicator having a superficial area of 100 square centimeters. Radium em-

Fig. 160.—Sycosis vulgaris.

Fig. 161.—Patient in Fig. 160 after removal of hair with radium.

anation tubes may be arranged on this applicator in the ratio of 1.25 mc. per square centimeter. Screened with one millimeter of silver and at a distance of one centimeter, an exposure of forty-five hours may be given in three periods of fifteen hours each. Temporary alopecia results.

CHAPTER XVIII

RADIUM IN OPHTHALMOLOGY, OTOLOGY, RHINOLOGY AND LARYNGOLOGY

OPHTHALMOLOGY

A. Malignant Tumors

Epithelioma of the Eyelid has been referred to in the chapter on Radium in Dermatology.

Epithelioma of the Conjunctiva has been successfully treated by Wickham and Degrais and others.

Sarcoma of the Orbit has been considered in the chapter on Radium in General Surgery.

B. Vernal Conjunctivitis

In vernal conjunctivitis radium is of considerable value. Sometimes the most rebellious cases are completely relieved. Treatment should be carried out cautiously. A "full strength" applicator unscreened may be employed and a fifteen minute exposure given. In two weeks the exposure may be repeated, but only if inflammatory reaction has been slight or absent. Instead of the above type of applicator radioactive deposit may be collected on lead foil and used in a similar manner. Abbe, Allport, Butler, Davidson and Lawson, Schnaudigel, Shine, Shumway, and many others have reported successful results.

C. Trachoma

Radium is often of benefit in this intractable condition. The technic is similar to that suggested for vernal conjunctivitis.

D. Cataract

Cohen and Levin have reported upon the use of radium in twenty-four cases of immature cataract and claim improvement in 87.5 per cent of the cases. Twenty to forty milligrams of radium element were used. Gamma rays only were utilized. The radium was applied over the closed eyelid at a distance of two centimeters for two hours.

W. S. Franklin and F. C. Cordes have apparently confirmed these results. These authors have treated thirty-one cases of immature cataract of which 84.3 per cent showed a change for the better ranging from an improvement of three to four letters on the test chart to a complete disappearance of the process. They used the following technic. At a dis-

tance of 1.2 cm. from the eye, 10 mg. hours were given twice a week for four weeks and then once weekly until the process was stationary. The gamma rays from about ten milligrams of radium element contained in a glazed plaque having an area of 50.26 square millimeters were utilized.

OTOLOGY

In granulomata and papillomata in the external auditory canal, radium is frequently of great value. I have treated a number of cases in which recovery has been brought about. Fifty millicuries screened with 0.5 mm. of silver plus 0.5 mm. of gold may be used in the external auditory canal for six hours in periods of one hour each on alternate days. In "tinnitus aurium" radium has not been of marked benefit. Little improvement can be expected from the treatment of "chronic deafness" due to middle ear disease. I have treated in conjunction with O. T. Freer a number of cases of this character without definite benefit.

RHINOLOGY

Carcinoma and sarcoma of the nasal passages have been considered under Radium in General Surgery. In chronic ethmoiditis with recurring polypoid degeneration, radium has been used with good results by O. T. Freer and T. Melville Hardie. A platinum tube having a wall thickness of 0.3 mm. and containing 50 mc. of radium emanation may be inserted into the ethmoid sinus for five hours in periods of an hour each.

LARYNGOLOGY

A. Malignant Growths of the Larynx

Carcinoma and sarcoma of the larynx have been mentioned under Radium in General Surgery. The technic of intralaryngeal radiation is described below.

B. Benign Growths of the Larynx

1. **Papilloma of the Larynx.**—Abbe has reported a remarkable and successful case of papilloma of the vocal cord in which complete relief was obtained. The singing voice was restored and recovery has been maintained for more than ten years. In this patient a preliminary tracheotomy was performed and anesthesia was continued through the tracheotomy opening during the radium application. One hundred milligrams of radium were applied, by means of a wire passed through the tracheotomy wound into the mouth, for thirty minutes.

In a personal communication to the writer, Abbe states that other similar cases have since been treated and have done equally well.

G. B. New, of the Mayo Clinic, states that "the treatment of multiple papilloma of the larynx in children has been improved wonderfully by the addition of radium.

"The patient is suspended with the Lynch suspension apparatus, the papillomas are cleared out, and while thus suspended the radium is placed in the larynx in children with tracheotomy."

2. **Angioma of the Larynx.**—G. B. New, of the Mayo Clinic, has reported the results of the treatment of an angioma of the larynx occurring in a child. The growth caused "dyspnea which would have been very difficult to benefit in any other way. The angioma was entirely cleared up by the external application of radium."

3. **Chronic Infections. Laryngeal Tuberculosis.**—The results of treatment of this condition have varied. In a case of laryngeal tuberculosis treated in conjunction with Dr. O. T. Freer several years ago the result was not favorable. In this case the radium was held in the larynx by means of an intralaryngeal applicator. Fifty milligrams screened with one millimeter of silver was applied in periods of ten to fifteen minutes each, a total exposure of three hours being given. In another case in which two small lesions were present on the right vocal cord complete resolution was obtained by external applications. In this case, two hundred millicuries screened with two millimeters of lead and placed at a distance of two centimeters were applied for thirty hours in periods of fifteen hours each.

Technic of Laryngeal Applications.—*Surface Radiations over the Larynx.*—It is frequently possible to influence favorably benign and malignant tumors of the larynx by surface radiations alone. Benign tumors may be cured by surface radiations alone but malignant lesions require intralaryngeal radiations as well. At a distance of 3 cm., 250 mc. screened with 2 mm. of lead may be applied for twenty hours in periods of ten or more hours each. Four hundred mc. may be applied at a distance of 6 cm. for thirty hours in several periods.

Intralaryngeal Radiations.—In the technic of intralaryngeal radiations, a strong vise-like clamp (Fig. 162) is fastened to the forehead by a strap acting as a head-band. A metal forehead plate serves as a base for the clamp. Long stemmed applicators (Fig. 163) made of copper tubing ending in a holder (Fig. 164) securely grasp the screen containing the emanation tube which is thus placed exactly upon the desired area in the larynx. In making a laryngeal application the larynx is first anesthetized with cocaine flake crystals made into a mud by contact with a slightly moist swab. The local anesthesia is then reinforced with anesthesine powder insufflated into the pharynx and larynx. In order to introduce the emanation tube into the larynx, the applicator is seized by the thumb-plate (Fig. 163) and the screen is inserted into the larynx with the aid of the laryngeal mirror. Except in the case of papilloma of

the larynx in children, neither direct laryngoscopy nor suspension laryngoscopy is needed. When the screen has been introduced into the larynx, an assistant passes the stem of the applicator into the space between the jaws of the clamp which he closes upon the applicator stem, thus fixing the screen in place. Usually the tube may be retained for

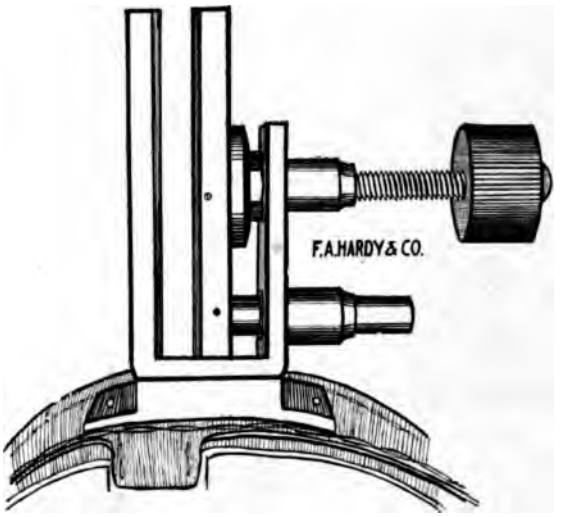

Fig. 162.—The Freer clamp for the intralaryngeal application of radium. The clamp seen from above affixed to the forehead plate of the head-strap and open to receive the tubular stem of the applicator.

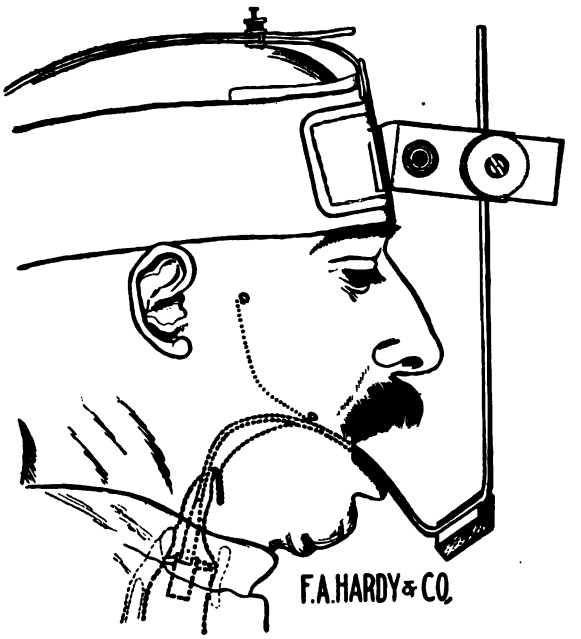

Fig. 163.—The applicator held in the jaws of the Freer clamp with the screen containing radium emanation in the glottis as indicated by heavy dotted lines.

from ten to sixty minutes without retching or distress. The hollow stem carrying the emanation tube is attached to an electric suction pump which serves to keep the throat constantly free of saliva and secretions. The use of moderately large doses is of great value in the treatment of feeble patients. An exposure of 400 mc. hours may be given in the course of a week or more.

With intralaryngeal and surface radiations combined I have treated, in conjunction with Dr. O. T. Freer, 19 carcinomata of the larynx. Of these 5 were extrinsic, 14 intrinsic. Clinical recovery has occurred in 9 of the intrinsic and in one of the extrinsic cases, and has been maintained for from 2 to 12 months. One case recently developed a metastasis in the humerus but the larynx is clinically well. Of the remaining

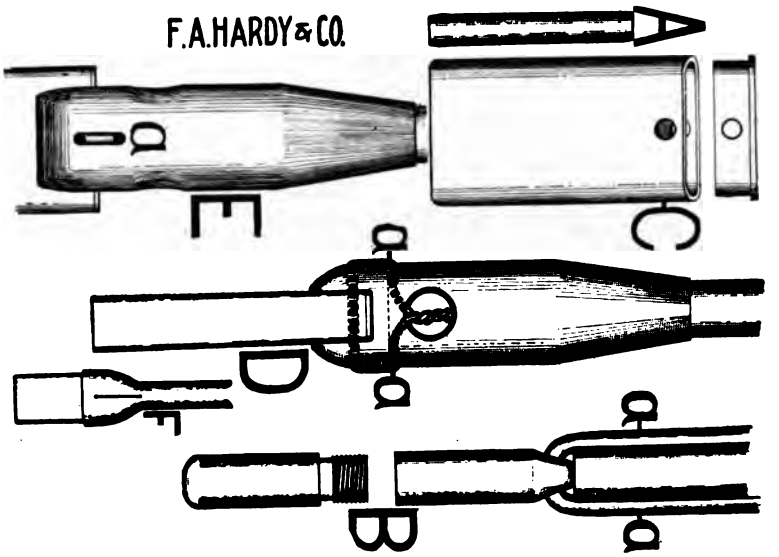

Fig. 164.—*A*, Enamel silver tube containing capillary glass emanation tube: *B*, Screen fastened to tubular copper applicator at *a*—*a* by means of copper wire soldered into grooves at sides of applicator and run through eye of screen. Screen holds one enamel tube only; *C*, silver screen with cap; wall thickness of screen 1 mm. These screens hold from 2 to 6 emanation tubes and are identical with the screens used for surface radiation previously illustrated; *D*, silver screen seen on edge, fastened into notch of holder by No. 24 copper wire *a*—*a* shown by heavy dotted line to indicate passage of wire through holes passing through jaws of notch, walls of screen, and its cap and thence into interior of tubular holder through holes at *a*—*a*. The wire is shown twisted in the saliva hole of the holder in order to lock the screen safely to the holder; *E*, holder and screen seen on the flat to show the holes at (*a*) connected by a groove, the holes being bored to pass copper wire through jaws of notch, screen, and its cap and thence into the interior of the tubular part of the holder; *F*, socket holder to hold screens for use in the glottis. The holders must be individually made to fit each screen. The advantage of this holder lies in the firmness with which it grasps the screen.

9 patients, seven were too far advanced for more than palliation and two who have been under treatment for only a short time were also of the advanced type. In one case of multiple papillomata of the right vocal cord and in one case of diffuse, hypertrophic laryngitis with great deformity accompanied by loss of voice for fifteen months, complete recovery occurred. In both cases the voice was restored and the larynx shows no trace of the pathological process, the cords appearing white and normal.

A rapidly growing sarcoma of the right vocal cord recently under treatment completely disappeared leaving the larynx nearly normal except for some cicatricial retraction. Relapses are to be anticipated in a certain percentage of the cases of malignant tumors of the larynx.

The intralaryngeal treatment is usually reinforced by deep gamma radiations applied to the surface of the skin over the laryngeal region. The applicators and the technic of intralaryngeal radiations which we have just described have been devised and made of practical utility by Dr. Otto T. Freer.

Hypertrophy of the Tonsils

C. A. Simpson, W. A. Wells, the writer, and others have found radium of value in the treatment of certain cases of hypertrophied tonsils.

Simpson has used a double strength dermatological applicator containing 30 mg. of radium element. This was wrapped in rubber dam and applied unscreened for one hour. Wells has inserted radium contained in metal needles into the tonsil. In some cases, 100 mc., screened with 1 mm. of silver plus 1 mm. of rubber may be applied for 1 hour to each tonsil. The normal tissues of the throat must be carefully protected.

In selected cases, radium treatment may be substituted for operative removal of the hypertrophied tonsil.

CHAPTER XIX

RADIUM IN DISEASES OF THE DUCTLESS GLANDS

A. LEUKEMIA

Renon, Degrais and Desbouis were among the first to use radium in the treatment of myelogenous leukemia. The radium was applied directly over the spleen. After referring to twelve cases treated by other French workers, these authors reported five cases under their own care in which satisfactory remissions were obtained. Of the five cases reported, death occurred in two, two years and two months after the first exposure. Two cases were in good health six months after the first treatments. In the fifth case, splenectomy had been performed prior to the radium treatments. In spite of this, however, radium applied over the splenic area produced a marked decrease in the leucocytes, which fell from 143,000 to 21,500. This effect may be accounted for, most probably, by the exposure to the rays of the large volume of blood circulating in the cavity of the abdomen. Later, Renon, Degrais and Tournemelle reported a sixth case of leukemia in which radium was used with benefit. Numerous cases have been reported more recently by Giffin, Hayward Pinch, Ordway, Peabody and many others, including myself, in which a favorable influence has been exerted by radium. Giffin has reported thirty cases and Peabody has observed thirty-six cases of leukemia in which radium treatment was used. I have treated fifteen cases.

All of the cases just referred to were treated in the usual way, i.e., by the surface application of the radium over the spleen.

The beneficial effects of the radium treatment of leukemia are quite uniform.

A certain degree of improvement occurs in the general condition of practically all of the cases. Headache may be relieved and the "buzzing" in the ears sometimes complained of may disappear. In certain cases the improvement in the general condition is quite remarkable. Even in the bedridden, sufficient improvement in the appetite and strength may occur so that the usual occupation of the patient may be resumed. The effect on the spleen is to reduce it perceptibly in practically all cases. Frequently the spleen becomes almost or quite nonpalpable. The spleen usually shows the greatest reduction in size in about one or two months from the beginning of the treatment.

The blood picture shows very definite effects of the treatment. The number of leucocytes usually begins to decrease in from one to three days after radium is applied and may progressively continue to diminish for several days or even weeks after the exposure. In one of Peabody's

cases of myelogenous leukemia in which radium was applied on the first and thirteenth days only, the leucocyte count fell from about 100,000 to 6,000 in twenty-five days. In a case of chronic lymphatic leukemia, previously reported by the writer, the leucocytes fell from 113,000 to 5400 in 28 days. Many other even more striking illustrations of the

Fig. 165.—Chronic lymphatic leukemia. Greatly enlarged cervical and axillary lymphatic glands. White blood count 113,000. Photograph taken January 12, 1917. Patient referred by Dr. Charles A. Elliott.

improvement in the leucocytosis might be cited. With regard to the differential leucocyte count, the relative as well as the absolute percentage of myelocytes is usually strikingly reduced. The relative percentage of neutrophilic polynuclears remains about the same but the abso-

lute number is usually markedly diminished. The relative percentage of small lymphocytes shows an increase after the reduction in the leucocyte count but the absolute count of the small lymphocytes is much diminished. The relative percentage of large mononuclears is usually increased.

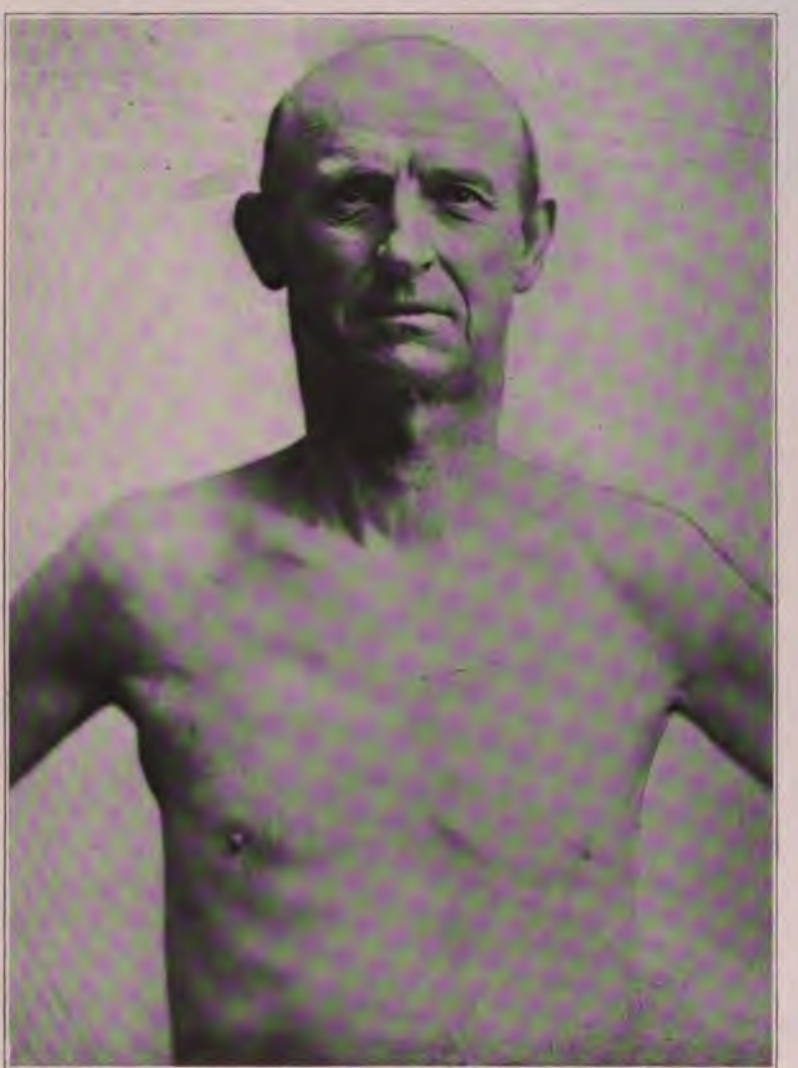

Fig. 166.—Patient in Fig. 165 showing remission of the disease after radium treatment. The cervical glands have become practically normal and the axillary glands are markedly reduced. White blood count 7,500. Photograph taken February 3, 1917.

In the majority of patients, there is usually an improvement in the red blood count and in the percentage of hemoglobin. If hemorrhage, such as epistaxis, purpura, etc., is present it usually ceases. While it has been held by some that hemorrhage may even be caused by radium treatment,

I believe this to be very unlikely. In any series of cases, hemorrhage may occur, but as it is a symptom that is not uncommon in the natural course of the disease, it is difficult to ascribe it to the effects of radium.

Technic of Treatment.—The best guide to the amount of treatment is furnished ordinarily by the condition of the white blood count. One should not attempt to bring the leucocytic count down to normal. Probably a count ranging between 15,000 and 30,000 will be found to accord with a satisfactory clinical condition. Peabody has stated that patients seem to do well clinically if their white count is not over 50,000. Excessive radiation may result in actual harm.

The technic of the application of radium is simple and while similar results may be obtained by different methods, it is our belief that too large doses should be avoided. The radium may be applied to different areas of the spleen successively, or to the lymphatic glands, as the case may require. Although some advocate radiation of the long bones in myelogenous leukemia, this has not been thought advisable, nor in our experience necessary in order to produce remission. Ordway used, in one of his cases, an applicator of about "double" or "triple" strength (50 to 60 mc. concentrated on 4 square cm.). With this apparatus the spleen was covered by radiating successively every 9 square centimeters of skin surface. The metal filter was 3 millimeters of lead and the distance (obtained by 15 to 20 thicknesses of filter paper or 25 to 30 layers of gauze) was apparently about 5 to 10 mm. additional. Exposures of four to six hours over each area were given. Three series of treatments were given four to six weeks apart. Great symptomatic improvement followed, although the patient died about eight months after the first series of treatments. Giffin has used a technic similar to that just described. Fifty to one hundred milligrams of radium element were employed. The screening finally used was two millimeters of lead plus one half inch of wood. The enlarged spleen was mapped out into squares 3x3 cm., each square receiving successively two to four hours' radiation. The total length of time for the complete radiation of the spleen varied from twelve to forty-eight hours, the usual time being twenty-four to thirty-six hours. The exposure was repeated every week until remission was progressing satisfactorily. Peabody has stated that the experience of himself and his coworkers does not enable them as yet to state definitely the best dosage. There is some evidence, however, leading them to believe that one or more powerful treatments followed by an intermission of several weeks until the effects of the radium are over, are preferable to repeated small doses. My experience leads me to prefer this latter method. Ordinarily 200 millicuries (1¼ mc. to each square cm.) screened with 2 millimeters of lead and at a distance of 3 centimeters may be used. An exposure of six hours twice weekly may be given over successive areas until the splenic area, or in lymphatic leukemia, the area over each group of lymphatic glands has been covered

or until a satisfactory diminution in the leucocytes is evident. The course may be repeated in six weeks but may be given earlier or later as thought advisable. It must be emphasized, however, that great judgment is required in determining the size of the dose and the frequency of its repetition. Various factors must be considered, these being principally the effect of the treatment on the general condition, on the size of the spleen and especially the effect on the white blood count. Radium, applied to the spleen in the manner indicated, may cause a constitutional reaction, such as nausea, vomiting, malaise and headache. These symptoms usually pass off within twenty-four hours. An excessive amount of treatment may result in marked leukopenia and an increase in the anemia. These symptoms should be guarded against by caution in repeating the exposures. If they do occur or if hemorrhage supervenes, transfusion should be resorted to. Locally a skin reaction may occur, but with the technic advised this will be slight or absent.

In applying a radium pad to the splenic area, the outer aspect of the pad should be protected so that the patient's arm will not rest inadvertently on the radium tubes.

Results of Radium Treatment of Leukemia.—Complete remission or at least a satisfactory clinical condition may be expected in from three weeks to three or four months. Patients may remain apparently well for several months or even several years. Recurrences may take place but these usually yield, at least for a time, to further treatment. Surgical removal of the spleen is probably advisable in selected cases when the remission of the disease is at its height.

In twenty of Giffin's cases, eighteen of which were treated with radium, splenectomy was performed when the reduction in the size of the spleen rendered the operation advisable. One patient died as the result of operation. Ten patients were living and in good general condition, nine to nineteen months after the splenectomy. Giffin concluded, however, that the natural course of the disease was probably not altered by splenectomy, although the patients may be made more comfortable by the operation.

In addition to the usual method of treating leukemia by exposing the spleen or lymphatic glands to surface radiations, a few workers have investigated the effects of radium when administered constitutionally. The results of this method of treatment have varied. Von Noorden and Falta did not obtain beneficial results from the inhalation of radium emanation. Proescher and Almquest injected soluble radium salts intravenously but without marked benefit. Falta, Kriser and Zehner obtained remissions in leukemia by the injection of thorium X, the action of which is similar to that of radium. Radioactive deposit dissolved in water has also been injected by a few workers. For the present, however, the method of treatment of leukemia by exposure of the spleen or lymphatic glands to surface radiations is to be preferred. Radium treatment is probably the method of choice, in the treatment of leukemia at the present time. It

sometimes succeeds in producing remission when all other methods, including the use of benzol and x-rays, have failed.

B. HODGKIN'S DISEASE (LYMPHADENOMA)

The affected glands in Hodgkin's disease frequently disappear very promptly. In only one of eleven cases treated have we seen rebelliousness to the treatment. In two cases of that form of the disease, in which nodular tumors appear on the bones (sternum, skull bones, etc.) very marked susceptibility to the radium rays was noted. In several cases we have seen remissions which have persisted for more than one year. It is probable, however, that recurrence takes place sooner or later in most cases. The treatment is ordinarily given by means of deep radiations. The enlarged glands may be treated serially in order to spare the patient as much as possible the systemic reaction (nausea, malaise) which frequently follows heavy doses.

Four hundred millicuries screened with 2 millimeters of lead may be used at a distance of 6 centimeters for a total of 30 hours in periods of ten or more hours each over each area. The concentration of the radium may be 5 mc. per square centimeter. Treatment may be given twice weekly or less often until the areas involved have been radiated. Occasionally less powerful treatments may be given for three or four days in succession if the systemic disturbance is slight.

C. GOITER

In the various types of goiter, radium treatment may be helpful.

In the simple parenchymatous type there is general enlargement of the thyroid gland and the follicles, which are usually newly formed, contain colloid material. The results of radium treatment in this type may be very beneficial.

The vascular type of enlarged thyroid may also respond well. In favorable cases the neck may decrease in size several centimeters.

In the type of goiter in which large cysts occur, the walls of the cysts frequently undergoing calcification, but little benefit is to be expected from radium treatment.

Exophthalmic Goiter

Abbe, of New York, treated the first case of this disease with radium in 1905. Following Abbe's report many other authors, including Aikens, Burrows, Clagett, and Dawson Turner have reported favorably upon the results of radium treatment. Radium may be used when the ordinary methods of treatment prove unavailing or when operation is considered inadvisable. In cases that respond favorably, improvement in all the toxic symptoms may be noted in three to six weeks and in some cases, very much more quickly. Tachycardia, tremor and exophthalmos are

frequently diminished. The high blood pressure which is so frequently present is often diminished and after several courses of treatment may become practically normal. In some cases operation may be performed if thought advisable after a certain degree of improvement has been brought about by radium. It has been held that operation is rendered more difficult by previous radiation. It must be remembered that striking remissions may occur in the natural course of the disease so that it is sometimes difficult to judge of the effects of treatment.

Technic of the Treatment of Goiter.—The method of treatment involves the use of moderately deep penetrating rays. Aikens, who has observed about one hundred cases, advises in the beginning of treatment a total exposure of from 150 to 360 milligram hours. Subsequent courses of 50 to 150 milligram hours may be given. Many other authors use larger doses than those just indicated. I ordinarily use not less than 150 millicuries, screened with 2 millimeters of brass and placed at a distance of 3 centimeters. Five millicuries may be concentrated on each square centimeter. A total exposure of twenty hours on each of three areas is given. In certain cases of large goiters we use 500 millicuries concentrated on an applicator having a superficial area of fifty square centimeters. This is screened with 2 millimeters of brass and applied at a distance of 6 centimeters. An exposure of fifteen hours may be given to each lobe and to the isthmus of the thyroid. The three exposures should be given several days apart. Depending upon the severity of the disease, the dose may be diminished or increased in different instances. In some cases, following the treatment there is an exaggeration of the symptoms for several days or even for a week or more. Improvement then usually sets in and by the end of a month or six weeks may be very decided. The course of treatment may be repeated at intervals of six or eight weeks. Subsequent courses of treatment may be of less intensity. The amount of treatment may be regulated by the basal metabolism test.

In addition to the radium treatment, supplementary measures including rest, diet and suitable drugs should be used.

D. ENLARGED THYMUS GLAND

Brayton and Heublein have treated with radium 34 cases of enlarged thymus gland in children. In every instance there followed a prompt and lasting disappearance of all symptoms. These authors state that "every infant who has 'queer spells' who has habitual attacks of coughing, choking, dyspnea, or cyanosis should have an x-ray examination of its chest in the hope of finding a condition (pathologically enlarged thymus) which is so easily and satisfactorily cured." Their technic consisted in using 100 miligrams of radium element screened with 0.5 mm. of silver. The radium was applied at a distance of one half inch from the skin to four different points over the thymic area and allowed to remain for two hours over each point.

CHAPTER XX

RADIUM IN INTERNAL MEDICINE

Radium and thorium X are the two principal radioactive substances used in internal medicine. The biologic action of these two substances is similar but not absolutely identical. Proescher states that while all radioactive substances produce a more or less marked numerical increase of the red blood cells, thorium X is the only one causing pronounced destruction of the leucocytes. The more rapid decay of thorium X as compared with radium explains its more intense biologic effect. The investigations of the effects of thorium X have enabled us to fill up some of the gaps in our knowledge of the effects of radium. In the following pages its action will be considered in connection with that of radium.

We may discuss the internal administration of radium under the following headings: (a) the administration and elimination of radium, (b) its physiologic effects, (c) morphologic changes in the tissues caused by radium, (d) therapeutic indications.

A. THE ADMINISTRATION AND ELIMINATION OF RADIUM

(1) The Administration of Radium

Radium may be administered either in the form of radium salts, radium emanation or the active deposit. The effects of both the salts and the emanation appear to be practically identical except that the action of the emanation is naturally more evanescent and therefore perhaps more desirable on account of the rapid elimination from the body of a gaseous element. Less experience has been had with the actual administration of the active deposit but it seems probable that the effects are the same as those of the salts and the emanation.

Administration of Radium Salts

Radium salts are usually administered by giving, by mouth, water containing the salt in solution or by the injection of a solution of the salt intravenously. The drinking water is usually of a strength of one microgram of radium element to 30 c.c. of distilled water. The ordinary dose is 120 to 240 c.c. per day. For injecting intravenously, 10 to 100 micrograms of radium element in the form of a soluble salt dissolved in 2 c.c. of normal salt solution may be used. Injections are usually given every week or ten days until the patient has received 300 micrograms.

Administration of Radium Emanation

Radium emanation may be administered by means of drinking water in which the emanation is dissolved, by inhalation, or by baths. Radium emanation in solution may be given by mouth. The strength of "emanation drinking water" is usually 1.5 to 2 millicuries per liter of water. About 250 c.c. is the usual daily dose. If the inhalation method is used the patient may sit in a small room known as an "inhalatorium," the air of which is impregnated with the emanation mixed with oxygen. The air which is breathed is purified by being passed over caustic soda and is then returned into the room. This is objectionable on account of the respiratory products which are continually being reinhaled. By another method, the patient inhales a stream of air or oxygen mixed with the emanation and exhales it into the open air by a valve arrangement. This is a better though more wasteful method. The quantity of emanation in the air inhaled varies from 0.003 to 0.3 microcurie per liter of air. Inhalation treatments may last an hour or more. The results of treatment by the inhalation method seem to differ in no wise from those obtained by the administration by mouth of emanation drinking water and the latter is certainly the more convenient and economical method. Gudzent, Falta and some others, however, make considerable use of the inhalation method. Emanation baths may also be given, but the good effects claimed seem to be due solely to the emanation that is inhaled.

Administration of Radioactive Deposit

H. J. Bagg has investigated the pathologic tissue changes accompanying the injection of the active deposit. White rats were injected intravenously and subcutaneously. Pathologic changes in the various organs—liver, lungs, kidneys, adrenals, spleen, bone marrow, brain and vascular system—were noted and described in detail. Among the effects were fatty degeneration in the liver, granular degeneration and erosion of the kidney cells, destruction of the cells of the bone marrow and their replacement by blood, and congestion and hemorrhages in practically all of the organs. A similarity was noted in the tissue reaction due to radium applied externally and that due to the active deposit when injected subcutaneously or intravenously. Doses of less than ten millicuries of radium emanation were not fatal to the experimental animals. Larger doses caused death within a few hours or days. The doses used in human beings have varied from fifty to two hundred and fifty millicuries of active deposit dissolved in two to six c.c. of solution. In one case severe toxic symptoms developed after the injection of 250 mc. Similar doses in other patients produced no ill effects.

(2) The Elimination of Radium

From our knowledge of its chemical affinities it would be expected that radium, when held in the body, would be found wherever the other

alkali earth elements are found, inasmuch as radium is an element closely akin to calcium, barium and strontium. According to Seil, Viol and Gordon, analysis of the dead tissues of animals and humans who have had radium administered has shown that the bones, as might be expected, do contain the highest concentration of radium. Following the bones, in the order of radium content, come the liver, lungs, blood vessels and spleen. Cameron, Viol and Proescher examined dead tissue from a human being who had suffered from uterine cancer. The patient had received 1 mg. of radium element intravenously 3 months prior to her death. These authors found that the cancerous tissue did not contain a greater relative amount of radium than other tissues and not as much as the bones and some other organs.

The method of the elimination of radium has been studied by Bellingham-Smith, Brill and Zehner, Seil, Viol and Gordon, and many others with general agreement as to the main trend of the observations. Bellingham-Smith found that radium injected into mice was excreted principally by the small and large intestines and to a lesser extent by the urine. According to this author, soluble salts, however administered, are rapidly eliminated, mainly by the intestine, but also by the urine. Insoluble salts, given by the mouth, are directly excreted by the bowel without being absorbed, but when given by injection are excreted very slowly by the bowel. After administration of the emanation in solution, a general but brief radioactivity is caused throughout the organism. Elimination, which takes place almost entirely by the lungs, and to a very slight extent by the kidneys, is complete in 4 hours. Ketron found that only a very minute quantity (0.025 micrograms) was eliminated by the skin after the intravenous injection of 100 micrograms. Seil, Viol and Gordon have made one of the most extensive studies of the excretion of soluble radium salts when administered both intravenously and by the mouth. The following conclusions were reached by these authors: The principal part of the radium is excreted by the feces with either method of administration. Most of the remainder is eliminated by the urine. A minute amount is eliminated by the lungs in the form of radium emanation which is being constantly formed by the disintegration of the radium held in the body. As might be anticipated, when radium is administered by the mouth a smaller proportion of the excreted radium is eliminated by the urine than when it is injected intravenously. From 25 to 35 per cent of the radium taken by mouth remains in the body for 4 or 5 days after ingestion. If radium is injected intravenously, 55 to 65 per cent remains for the same length of time. From this time on, the rate of elimination is about the same whether ingested or injected. By the 10th day the daily rate of excretion is less than 1 per cent. As a result, there is an exceedingly slow elimination of the balance of the radium, the process going on for months. The first rapid elimination

takes place before the radium has become "fixed" in the tissues. When "fixation" of the radium has taken place all methods of elimination are much slower. By fixation is meant that the radium that is not eliminated at once is probably carried in the blood stream in solution or suspension until it becomes absorbed by the various tissues in proportion both to their alkaline earth salt content and to their accessibility by the blood. On the basis of the foregoing studies, these authors suggest a rational method of maintaining radium in the system. If, for example, it is desired to maintain about 50 micrograms of radium element in the body, one may give an intravenous injection of about 100 micrograms. After the lapse of about ten days, 2 micrograms may be given every few days by mouth to replace that which is eliminated.

B. PHYSIOLOGIC EFFECTS OF RADIUM

Experiments on different animals as well as on human beings to determine the effects of radium have been carried out by Bellingham-Smith, Cameron and Viol, Dominici and Faure-Beaulieu, Gudzent, Jaboin, Proescher, Salant and Meyer, Wickham and Degrais and many others.

We may first consider the effects of *therapeutic doses*. These effects may be discussed under the following headings. (1) the general physiologic effects, (2) the effects on the heart, circulation and respiration, (3) the effects on metabolism.

(1) General Physiologic Effects

One of the chief subjective benefits derived by many patients taking radium in therapeutic doses is a feeling of "bien être." Whether this is entirely subjective, it is, of course, difficult to say. In arthritic cases especially, a certain amount of relief from pain may be experienced. The majority of patients taking radium emanation solution have a definite diuresis and a slight laxative effect is sometimes observed. Some patients experience a definite so-called "reaction." S. Lowenthal first called attention to this phenomenon. The reaction is characterized by an aggravation of symptoms, after a certain amount of treatment has been given. There may be, e.g., an exacerbation of any joint symptoms that have been present. General disturbances, including "tired feelings," "malaise," and a desire for sleep, may occur. In other patients there may be excitement and sleeplessness. These symptoms pass off after a time if the treatment is discontinued. According to Gudzent, these phenomena are frequently of favorable prognostic import.

(2) Effects on the Heart and Circulation

The effects of a radioactive Ringer's solution on the isolated frog's heart have been studied by Maass who found that the heart became dilated and its action arrested. By rinsing out the heart with normal

Ringer's solution, its normal activity returned. The heart showed less activity with each experiment, indicating according to this investigator, a lowered resistance. In mammals, however, Plesch and Karczag could not duplicate these results. Zwaardemaker has described a new and hitherto unknown effect of the radiations on the heart. This author found that a frog's heart kept actively beating by artificial circulation ceased to pulsate if the potassium was extracted from the circulating medium. If the heart was then radiated with a few milligrams of radium for thirty minutes it again began to beat. If a certain quantity of uranium salt was added, the heart again stopped. Renewed radiation again started the action of the heart.

While these experiments are extremely interesting from a scientific standpoint, no therapeutic deductions have as yet been drawn from them.

Certain of the experiments on blood pressure have a practical aspect. In various experiments on dogs and human beings carried out by Loewy, Plesch and Gudzent with inhalations of radium emanation and injections of thorium X, the blood pressure in general was markedly decreased. According to Gudzent, the decrease in blood pressure, which may be lowered for long periods and may even become and remain normal in certain gouty and arthritic patients, is due to the destructive effect on the vasoconstrictor substances produced by the suprarenal glands.

Respiration.—In animals and in healthy human beings, no especial effect on the respiration from therapeutic doses can be observed. In cardiac dyspnea and in pneumonia, Plesch has reported an acceleration and increase of respiration.

(3) Effects on Metabolism

The influence of the administration of radium on metabolism has been studied by Falta, Gudzent, Krieg, Lowenthal, Plesch, Rosenbloom, Wilke, and many others. The investigations tend to show that the excretion of uric acid and of purin is increased. The entire nitrogen excretion is also increased. Following an injection of one hundred micrograms of radium element intravenously, Rosenbloom found that there was a considerable increase in the ethereal sulphur output. In three patients whose metabolism while taking radium emanation water (3 ounces, five times a day or 20,000 Mache units in all) was studied by McCrudden, no marked metabolic changes were made out. Only one definite change was observed—a slight increase in the rate of creatinin excretion. The results of the studies of various authors have shown, in general, marked differences in the effect on metabolism and in some patients little or no effect has been observed. We may also mention here the investigations of Knudson and Erdos who studied the metabolism of a case of leukemia that was being treated by surface applications of radium over the spleen. The conclusions of these authors were as follows: The excretion of

nitrogen, urea, ammonia and phosphates was enormously increased after the application of radium. The uric acid output was only slightly increased compared to the other nitrogenous bodies. Surface applications of radium over the spleen accelerated the disintegration of nuclein tissues resulting in the increases mentioned above. An increased production of uric acid that was anticipated on account of the disintegration of nuclein was not observed. The effect on the phosphates was remarkable, there being at times an increase of four hundred per cent over the excretion observed at the beginning of treatment.

We may now consider the effects of *toxic doses* of radium. The following description of the effects of a lethal dose has been given by Gudzent: If an animal, e.g., a rat, receives an injection of a soluble radium salt of sufficient strength, no changes are at first apparent which indicate injury to the organism. The animal eats, sleeps, moves about, and passes urine and stools in a normal manner. In a few days, however, the picture changes. The animal appears to be ill, refuses food, and sits about in a "crumpled up" position. Its respiration increases, fever is present, and it passes bloody stools and urine. The animal then grows weaker and weaker and usually dies in convulsions. As to the exact cause of death it has been held that it may be due to the effect of the radium as a toxic substance.

Experiments with barium, an analogous chemical element, do not bear out this view. To cause death with barium one must use a dose several hundred times greater than the lethal dose of radium. The toxic symptoms are also dissimilar. The death of the animal, therefore, after a sufficient dose of radium internally, appears to be due solely to the effect of the radiations. Gudzent has estimated the lethal dose of radium when injected in the form of a soluble salt to be about .007 mg. of radium element per kilogram of body weight. For a body of 70 kilograms the fatal dose would thus be about 0.5 mg. According to the experiments of Cameron, Viol and Proescher, this estimate is low. These authors have carried out an extensive series of experiments with injections of soluble radium salts. They state that they have used doses as high as five milligrams of radium element in 2 c.c. of normal salt solution intravenously in human beings and have never seen from these doses the slightest ill effects. They regard doses of fifty to one hundred micrograms intravenously as therapeutically correct and absolutely safe. By the inhalation method, Proescher and Viol found that a concentration of 26 millicuries of emanation per liter of air (70 million Mache units) produced death in animals. Lazarus-Barlow exposed animals to the gamma rays of five grams of radium bromide. The minimum lethal dose of gamma rays for the rat was an exposure of six hours, the animal dying about forty-two hours later. For the rabbit an exposure of nine to ten hours was necessary.

C. MORPHOLOGIC CHANGES IN THE TISSUES CAUSED BY RADIUM

Inasmuch as the effects of radium taken internally are due to the action of the rays, one would expect that similar changes would be produced in the tissues whether the radium is administered internally or radiations are used externally. Experimental investigations have proved, in a general way, the truth of this supposition. There is, of course, this very evident difference: in the case of the internal administration of radium, the whole organism, and especially its most radiosensitive structures, is affected by the rays, but if radiations are used externally, the effect is practically limited to the part irradiated. By radiation of animals *in toto*, however, effects may be produced that are practically identical with those caused by the administration of radium.

We may now consider the changes produced in different tissues.

The Blood Vessels

Lethal injections into animals of thorium X produce an intense hyperemia of almost all the organs. Hemorrhages frequently occur; sometimes a single vessel is affected but at other times the hemorrhage may extend over large areas. The capillaries and smaller vessels show the most marked injuries.

The Blood. Leucocytes

If small doses of radium salts ($\frac{1}{1000}$ mg.) or thorium X ($\frac{1}{1000}$ to $\frac{1}{100}$ mg.) are injected intravenously or if inhalations of radium emanation (5 to 100 or more Mache units) are given, a transient leucocytosis appears a few hours later. The number of leucocytes may even increase to 20,000 (Gudzent and Levy). The next day, after a slight decrease to below the initial amount, the leucocytes become normal. If larger doses of thorium X (0.5 mg.) are injected, leucocytosis develops quickly. A leucopenia appears later. The leucocytes may decrease to 1000 or even lower according to the dose. If very large doses are administered the leucocytes may even disappear from the blood altogether just prior to the death of the animal.

According to Proescher and Almquest, thorium X has a more destructive effect on the leucocytes than radium. With superfatal doses of radium these authors were unable to destroy all the circulating leucocytes or myeloid cells of the bone marrow.

Erythrocytes

In contradistinction to the leucocytes, the red blood cells are not markedly sensitive to injections of radioactive substances. After small

doses, no change at all, as a rule, is seen. Sometimes, however, there may be an increase in number of erythrocytes as observed by Dominici in the horse and Brill and Zehner in dogs and rabbits. The last 2 authors found that the erythrocytes were increased in some cases to 13 million per c.c. This increase may be maintained for weeks. The hemoglobin was also increased but not proportionally to the increase in the number of erythrocytes. Proescher and Almquest have reported similar results. By the injection of larger doses of thorium X, the red blood cells may be damaged so that both a numerical decrease and a decrease in hemoglobin may occur.

In pathologic conditions, such as secondary and pernicious anemia, the erythrocytes appear to be more sensitive than in normal individuals. Proescher found that in such cases the injection of soluble radium salts (0.1 to 0.4 mg.) increased the red blood cells to normal in a few days. Gudzent has reported the same effect from the injection of small doses of thorium X (0.01 to 0.1 mg.).

Spleen, Bone Marrow and Lymphatic Glands

Gudzent states that the key to the understanding of the changes in the blood picture lies in the knowledge of the changes in the organs mentioned above which are, as we have seen, very radiosensitive. The changes produced by radium administered internally are practically identical with those caused by external radiations. These changes have already been described in a previous chapter.

Suprarenal Glands

Falta and his coworkers and later von Domarus and Salle called attention to the changes produced in the suprarenal gland and its functions. Injections of thorium X produced, in general, degenerative changes together with hemorrhages in the cells of these organs. The blood pressure of the animals was reduced in consequence of the disappearance of the substances causing vasomotor constriction. The effects on blood pressure depended on the dose but both small and large doses, after an initial increase, caused a decrease. In certain cases, the blood pressure rose again but did not attain to the point initially present.

Other Organs

The effects of injections of radioactive substances on other organs—heart, kidney, pancreas, etc.—are much less pronounced than on the previously mentioned structures. Traces of injury to the cells of certain areas may be detected but these changes are never of a general nature. Functional disturbances probably occur but these have not been as yet sufficiently investigated.

Effects of Large and Frequently Repeated Injections

A problem of importance is that of the possible constitutional effects of large and frequently repeated injections. The experiments of Silva Mello tend to throw some light on this question. This author found that the injection of a single dose of thorium X, if not immediately fatal, might so injure an animal as to cause its death in the course of a few weeks or months. The most obvious effects that were observed in the meantime were (1) leucopenia, (2) anemia (decrease in erythrocytes and hemoglobin), (3) marked decrease in weight. Evidences of regenerative processes were observed also in the bone marrow. If such an animal received a second injection, which was not large enough to cause death by itself primarily, the animal quickly succumbed. The blood, spleen, bone marrow and lymphatic glands showed evidences of the greatest damage. It may be assumed that the animal was sensitized by the first dose.

Equally interesting were the results of repeated injections of thorium X into animals in doses that were not large enough singly to cause perceptible severe injury. In these animals a certain degree of resistance apparently developed. Considerable quantities could be borne without any of the previous symptoms (leucopenia, anemia, loss of weight) developing, until, after a time, the animals rather quickly succumbed. In these animals the spleen was the only organ showing marked effects. The bone marrow was nearly always unaffected.

Inasmuch as it may be assumed that the effects of repeated injections do not differ materially from those of repeated external radiations which are delivered over very extensive areas, these experiments show the need of caution in the use of powerful and repeated exposures for therapeutic purposes. They also suggest the need of care on the part of the operator who is handling large quantities of radium in order that he may avoid injury to himself from the persistent exposure to the rays.

D. THERAPEUTIC INDICATIONS

The fullest details as to the use of radium and other radioactive substances in internal medicine are to be found in the recently published monograph of Falta.

Among the many diseases in which radium has been used with alleged benefit are the following:

1. Arthritis deformans, articular rheumatism (subacute and chronic) and various other types of arthritis.

2. Gout.

3. Myalgia ("muscular rheumatism"), neuralgia and neuritis (sciatica, tabetic pains, etc.).

4. "High blood pressure," arteriosclerosis, angioneurotic edema, neuroses of the heart, myocarditis.

5. Certain chronic inflammatory and suppurative processes.

6. Bright's disease and diabetes.

7. Leukemia, Hodgkin's disease, and various forms of anemia (pernicious anemia, chlorosis, etc.).

8. Dermatoses (psoriasis, scleroderma).

9. Malignant disease.

1. **Arthritis Deformans.**—It has long been the custom for sufferers from chronic joint diseases to visit springs in different parts of the world and drink the waters. With the discovery that most of these springs contained radium emanation in solution it became of great interest to determine the effect of radioactive substances artificially prepared. It may be noted that none of the springs at the various health resorts contains more than the most minute quantity of radium emanation (about 1 to 30 millicuries per million quarts). It would seem, therefore, that radioactive substances in doses sufficient to produce definite physiologic effects might be of even greater benefit. Hayward Pinch (London Radium Institute) has reported very favorable results from the administration of radium emanation water especially in arthritis deformans. In this author's experience pain was relieved and the mobility of the joints was increased provided no bony or cartilaginous changes had occurred. In some cases the results were quite remarkable. Cameron and many others have also seen favorable results in various types of arthritis. Gudzent, who has made one of the most extensive reports, states that many different types of arthritis, including certain cases of gonorrheal origin, are benefited. The arthritides in children, according to the same author, react favorably in contradistinction to those in the aged which do not respond well. In the treatment of arthritis, in general, benefit appears in the favorable cases usually between the 3rd and 8th week. Some cases do well when the treatment is interrupted for a few weeks and is begun again. Unfavorable symptoms, such as a permanent aggravation of the joint disorder or albuminuria, which have been alleged by some authors to have been caused by the radium have never been observed by Gudzent.

2. **Gout.**—Falta, Gudzent and others have reported favorable results in the treatment of gout. The last named author states that of 86 cases who had exensive treatment (emanatorium inhalations, "drink cure"), 77 per cent to 89 per cent were improved and 9 per cent to 11 per cent unimproved. In the course of time, however, most of the patients experienced recurrences. In a few patients no return of the disorder had taken place when the report was made.

3. **Myalgia.**—Benefit has been reported in some cases of the above disorders, the pain particularly being relieved according to many individual reports (Falta, Gudzent, Sommer, Kemen, Strasburger, etc.). Gudzent has never seen benefit, however, in neuralgia of the trigeminus.

4. **High Blood Pressure.**—The reduction of high blood pressure has been observed by many authors. Gudzent states that in some cases the blood pressure may be permanently reduced. Other authors, however, doubt the permanency of any reduction that may occur. Hayward Pinch has seen good effects from the use of radium emanation drinking water in angioneurotic edema. In arteriosclerosis, neuroses of the heart and myocarditis, benefit has been reported by some authors. In the last named diseases, the field for possible error in the interpretation of results is, of course, very great.

5. **Chronic Inflammatory Processes.**—Lachmann states that he has seen good effects from the administration of radium in inflammatory disorders of the female pelvic organs. Several authors (Levy, etc.) have reported favorable results in the treatment of various disorders of the mouth, such as leukoplakia, pyorrhea, etc.

6. **Bright's Disease and Diabetes.**—Benefit has been reported by certain authors in these disorders.

7. **Pernicious Anemia.**—Proescher recommends, on the basis of some excellent experimental studies, the intravenous injection of soluble radium salts in pernicious anemia and other forms of anemia. Gudzent also has seen good results from the injection of thorium X in pernicious anemia, chlorosis, and secondary anemia. The favorable results in pernicious anemia, are of course only temporary. According to Failla good results have been obtained by the injection of the active deposit in leukemia and Hodgkin's disease. The use of external radiations over the spleen is so satisfactory that there seems to be a small field, at present, for the use of radium internally in these disorders. The improvement in leukemia by any method of treatment is temporary although remissions may extend over considerable periods of time.

8. **Dermatoses.**—Individual reports of good effects in psoriasis and scleroderma have been made.

9. **Malignant Disease.**—Good effects have been reported by some authors from the administration of radium in various forms of malignant disease. Failla has reported good results from the injection of the active deposit in lymphosarcoma. It seems to the writer that for the present at least we must rely in malignant disease solely upon the effects of local radiations with radium rather than upon its constitutional effects when ingested or injected into the body. The radiosensitiveness of certain normal structures, such as the spleen, renders it unlikely that the internal administration of radium will ever be of practical utility in the treatment of most types of malignant disease. Long before the tumor itself will be unfavorably affected, normal structures may be seriously injured.

The experimental work referred to above, i.e., the injection of active deposit, etc., is of course valuable from a scientific standpoint.

In the field of internal medicine, the evidence seems to indicate that radium may be of benefit in

(a) certain chronic joint disorders (notably rheumatoid arthritis and the joint disturbances of gout),

(b) high blood pressure,

(c) pernicious and other forms of anemia,

(d) certain painful affections, such as some forms of neuritis, which it sometimes seems to ameliorate.

There is so much possibility of error in estimating the value of radium when administered internally that many of the reports of benefit and cures must be accepted with the greatest caution until further experience has been accumulated.

CHAPTER XXI

PROFESSIONAL INJURIES DUE TO RADIUM

Both local and constitutional injuries may be caused by persistent exposure to radium rays.

LOCAL EFFECTS

We have already described the acute inflammatory phenomena known as the "radium reaction" that may result from radium rays that are allowed to act with sufficient intensity on the skin. The various manipulations required in making therapeutic applications render a certain amount of daily exposure to the rays almost unavoidable. As a result of these persistently repeated slight exposures, many workers suffer from a peculiar chronic dermatitis that affects especially the ends of the first two fingers and thumbs. The skin becomes roughened and loses its elasticity. Fissures and atrophic changes in the skin may develop. The nails become brittle and thin. Exaggerated longitudinal striation and splitting of the nails may occur. Tiny wartlike epithelial tumors may form on the flexor surfaces of the ends of the fingers and thumbs. These tumors vary in superficial extent from one millimeter to one-half centimeter or more and may project one or several millimeters above the level of the skin. They resemble a certain type of senile keratosis. They cannot be scraped off except with the greatest difficulty but when they are removed, a depression is left reaching nearly or quite to the corium. Even when removed they recur sooner or later and may persist for years becoming worse or better as the individual is more or less exposed to the rays. Fortunately there has not been observed as yet any tendency to the development of epitheliomata in connection with radium keratoses. Subjectively the affected finger ends may show "anesthesia, paresthesia of varying degrees, tenderness, throbbing and even pain. The persistence of such effects is noteworthy." (Ordway.)

CONSTITUTIONAL EFFECTS

Those who are exposed more or less continuously to the gamma rays from radium may show various systemic symptoms, such as headaches, malaise, "nervousness," attacks of dizziness, menstrual disorders, etc. The most common of these symptoms is probably a feeling of undue exhaustion noted at the end of the day. In women, menstrual disturbances may occur. At first menorrhagia may be present. The menstrual function may then become irregular and amenorrhea may result. Normal

menstruation returns, however, after a somewhat prolonged absence from radium work. Many workers in radium after a certain amount of exposure to the gamma rays develop definite blood changes. Gudzent and Halberstaedter examined twelve radium workers and found that blood changes were present in all. The effect on the white blood cells was shown by a relative and absolute lymphocytosis, which was present in every case. In two cases, the hemoglobin was decreased but the number of red blood cells was apparently not affected. It is probable that the lymphocytosis mentioned above was an early effect of the rays, analogous to the initial lymphocytosis noted after therapeutic injections of radium. Others who have studied the blood changes in radium workers have found that leukopenia is practically always produced by persistent exposure to the gamma rays. Mottram and Clarke investigated the leucocytic blood-content of twenty laboratory and clinical workers engaged in handling considerable quantities of radium. The polymorphonuclear leucocytic and the lymphocytic blood content of all were found to be decidedly below normal. The leukopenia manifested itself a few weeks after exposure. After a holiday of two months, the polymorphonuclear leucocyte and lymphocyte counts rose decidedly but fell again upon reexposure to the rays. Hayward-Pinch also found a leukopenia in radium workers. This author states that the total number of leucocytes may even fall as low as one thousand per cubic millimeter. The hemoglobin and number of red blood cells in radium workers are not as markedly or as constantly affected as the white blood cells. At first the hemoglobin may be slightly increased. Later it may be diminished. Sooner or later the number of erythrocytes is also decreased.

No connection between the leukopenia and any condition of ill health, can, at present, be traced, although the possibility of untoward effects must be borne in mind. The constitutional effects of the gamma rays can be minimized or obviated by a sufficient amount of care in handling the radium.

For the protection of those engaged in radium work, various devices have been installed. To guard against the local effects of the rays we use (a) special forceps of different patterns. One type resembles the ordinary surgical tissue forceps, except that the radium forceps are twelve inches long (Fig. 22).

With these the radium tubes as well as the large radium pads can be conveniently grasped. Another type of forceps has three prongs at one end, with which even the smallest tubes may be picked up and held securely (Fig. 23). (b) Special "holders" for screwing together the different parts of screens or other radium apparatus (Figs. 25 and 26). (c) A special instrument by means of which one may wrap up the radium tubes in dental rubber dam without handling them with the fingers

(Fig. 24). All metal instruments used in handling radium apparatus should be covered with rubber tubing. Since using these devices the local untoward effects of the radium have not been observed.

For guarding against the gamma rays which are the main cause of the constitutional effects we use (a) heavy lead "angle plates." These should be at least five centimeters thick and may be set in a table or shelf at which the technicians may sit while manipulating the radium tubes. We have devised also a movable apparatus for the protection of the operator. This consists of an upright heavy cast iron plate attached to wheels. The apparatus can be easily moved about so as to stand between the radium applicator and the operator (Fig. 34). (b) Baskets lined with lead for transporting the radium pads from the making-up room to the patient. The baskets may be carried about by means of a sling. By this procedure the radium is constantly kept at some distance from the body and the gamma ray effect on the spleen and other important organs is minimized.

In addition to these precautions we have found that it is imperative that radium workers should abstain from work for at least two days per week and should have frequent vacations of one or more months' duration.

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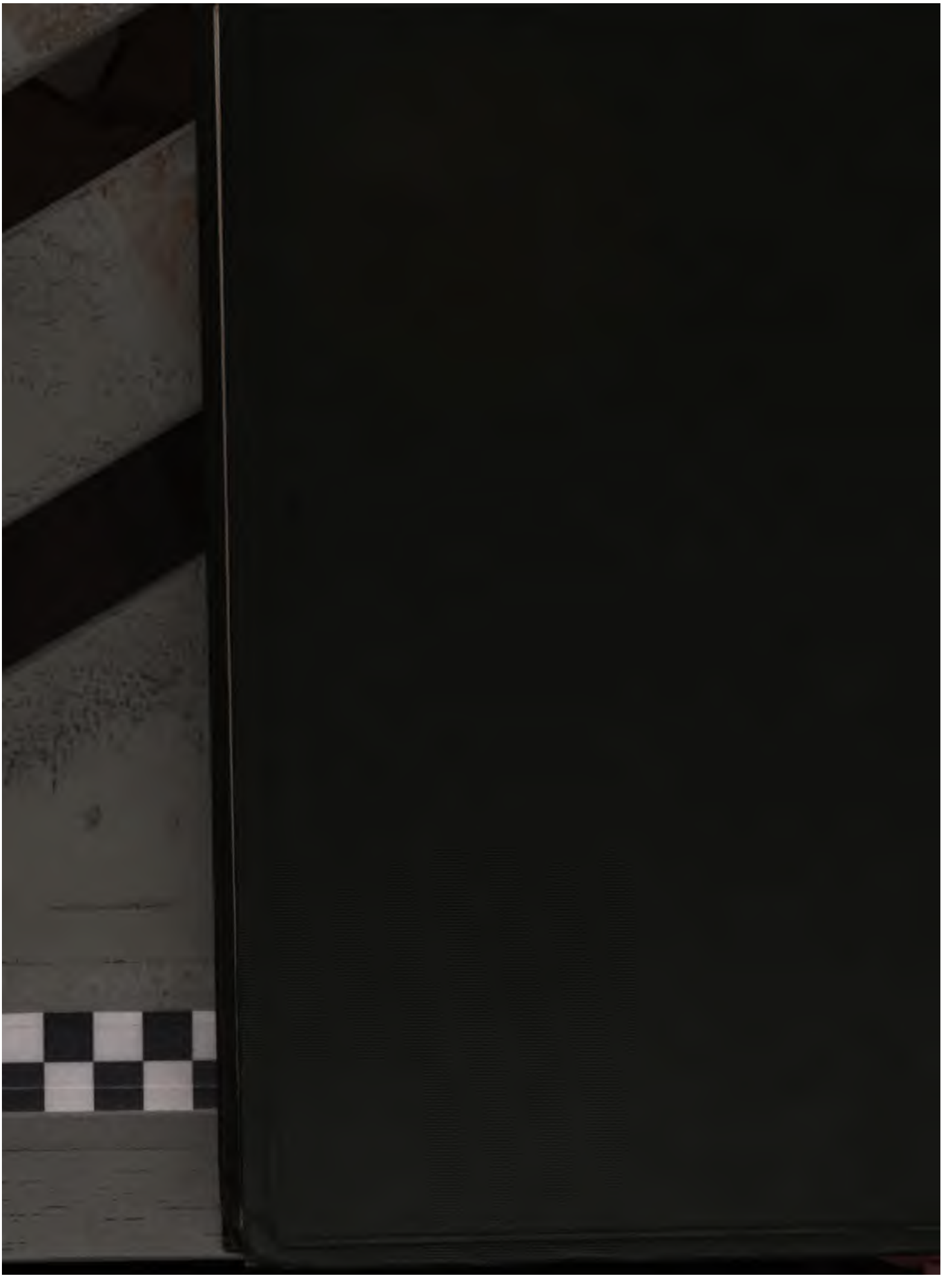
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